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TISSUE OXYGEN TENSION OF CERVIX CANCER

Comparison of effects of breathing a carbon dioxide mixture
and pure oxygen

by

PER BERGSJØ and JOHN C EVANS

The influence of varied inspired oxygen on malignant tissue radiosensitivity has been the subject of considerable research speculation and clinical investigation in numerous radiotherapy centers. It is quite well documented that many types of human cancer tend to outgrow their blood supply with consequent development of areas of hypoxic but viable cancer cells. These would presumably be less radiosensitive than the well oxygenated surrounding normal tissues. Attempts have been made to alter this situation by administration of 100% oxygen prior to irradiation at atmospheric or elevated pressure. Since the use of oxygen under high pressure is more time consuming and hazardous to the patient we have chosen to investigate the use of oxygen at atmospheric pressure in patients with carcinoma of the cervix. The present study was designed to determine the influence of adding carbon dioxide to the inspired oxygen on

From the Gynecologic Department (Director Oddmund Koller) of the Norwegian Radium Hospital (Director Reidar Eker) Montebello Oslo Norway. The investigation was in part supported by a Public Health Service Fellowship (No 1-F3-CA-19 559-01 to J C F) from the National Cancer Inst US Public Health. P B was a Fellow of the Norwegian Cancer Society. Submitted for publication 16 February 1967.

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tissue oxygen tension in the cervix cancers is determined by polarographic measurement

Several investigators have compared the use of a mixture of 5 % CO and 95 % O₂ to 100 % O₂ during irradiation of animal tumors. In experiments with spontaneous mammary adenocarcinomas in mice, DuSAULT (1963) found a higher cure rate following fractionated radiation treatment with the animals on a mixture of 5 % CO₂ and 95 % O₂ than with 100 % O₂. The proportion of mice with palpable tumor two months after irradiation was nearly as great after treatment with this mixture at atmospheric pressure as with oxygen at three atmospheres. INCH, McCREDIE & KRUVY (1966) treated two types of mammary carcinomas in mice, an 'isotransplant' which had been carried serially for many generations in C₃H mice, and an 'isograft' from a spontaneous C₃H mammary tumor to first and second generation offspring of the same strain. Only in the latter did the 5 % CO₂ mixture give a 'cure rate' (palpable at 100 days) greater than 100 % oxygen.

Assuming that these results could be explained through an increase in tumor blood circulation, a search for a possible CO₂ effect on the oxygen tension of human cancers seemed indicated. We have examined the oxygen tension in cancer of the uterine cervix by polarography in a large series of patients, and have continuously recorded changes in pO₂ with the patients breathing pure oxygen at one atmosphere's pressure. In an unselected group of these patients we have compared the effects of breathing 100 % O₂ with those of breathing a mixture of 5 % CO₂ and 95 % O₂.

Material and Methods

The *material* comprised 37 patients with carcinoma of the uterine cervix in clinical stage II (36 had squamous cell carcinoma, and one had an adenocarcinoma). Some of the patients were examined two or three times during the early phase of external irradiation, resulting in 55 different examinations.

The comparisons to be analyzed were carried out both before and during radiation treatment. As radiation induced changes in the tumor tissue could possibly influence the oxygen and carbon dioxide responses, the conditions at the time of the examinations are described, and the results analyzed separately.

Treatment commenced for all the patients with a series of 12 betatron fractions to external pelvic fields, and during this period the present investigation included three special examinations. Irradiations from 31 and 33 MeV beta trons were used, 200 R (Victoreen) skin dose per fraction, each fraction being delivered in about 10 minutes. Five to six fractions were given per week.

The first examination was made before treatment, the second examination



Fig 1 Electrode in position in tumor tissue Col
pophotograph according to the method of KOLLER
(1964) $\times 10$

after 775 R (Violereen) delivered in 5 fractions and 6 days the third exami
nation after 1700 R (Violereen) delivered in 11 fractions and 15 days These
average doses have been bas d upon the isodose charts and a mean estimated
tumor depth

The oxygen tension was measured directly in tumor tissue by means of bare
platinum micro-electrodes of 250μ diameter (The electrodes were kindly fur
nished by Mr Paul V Gabel of the Albert Einstein College of Medicine New
York N Y U S A)

The electrodes were placed superficially in the tumors guided by a Zeiss colpo
scope at 10 to 15 times magnification (Fig 1) This enabled the examiner to
see blood vessels down to capillary size distinctly and choose an avascular area
between vessels for placement of the electrodes As previously described the
distance between these superficial capillaries in cervix cancer is often greater than
 350μ (KOLSTAD 1964) The chance of hitting blood vessels below the tumor
surface was diminished by the very superficial position of the electrodes Active
bleeding was seldom observed either at the time of insertion or during the
recording when the electrodes were controlled regularly by inspection

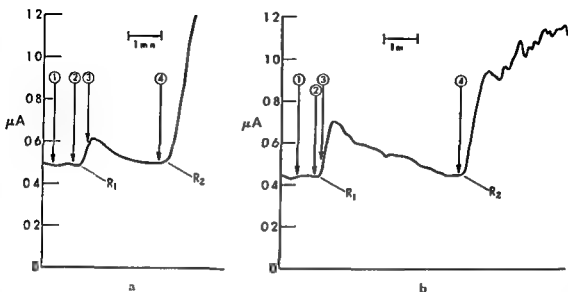


Fig 2 Determination of response times by continuous recording of the polarographic current. The symbols indicate 1—the patient breathes air 2—inhalation of 5 % CO_2 and 95 % O_2 starts R_1 —initial deflection from the control level distance between 2 and R_1 —response time 3—air breathing is resumed and when the original air breathing level has been reached at 4—100 % O_2 is administered R_2 —new point of deflection from control level

a) Code No 50 first examination In this case both response times were equal each measuring 9 seconds

b) Code No 51 second examination The response time for the CO_2 mixture was 12 seconds and for the 100 % O_2 it was 9 seconds

The vagina was kept open by a self retracting Cusco speculum, and the electrodes were kept in position in the tumor during the whole examination. A Polariter PO4 (Radiometer, Copenhagen) was used for recording the polarographic current and the silver coated Cusco speculum was utilized as reference electrode. By a sweeping voltage curve with the electrode in tissue, a plateau was noted to occur between -0.3 and -0.6 volts. The comparisons of maximum oxygen tensions were made with a fixed voltage of -0.4 V. Since bare platinum electrodes cannot be calibrated in absolute units of oxygen tension, change in tissue pO_2 are reported in units of microamperes (μA).

Experimental procedure A platinum electrode was inserted in the tumor tissue and polarized until a steady state current had been recorded. The gases to be compared, 100 % O_2 and the mixture of 5 % CO_2 and 95 % O_2 , were then administered alternately at atmospheric pressure through an ordinary anesthesia face mask. A Ruben valve prevented rebreathing of expired air. The patient was instructed, and the mask was applied tightly to the face.

The special examinations were time consuming, often lasting up to three

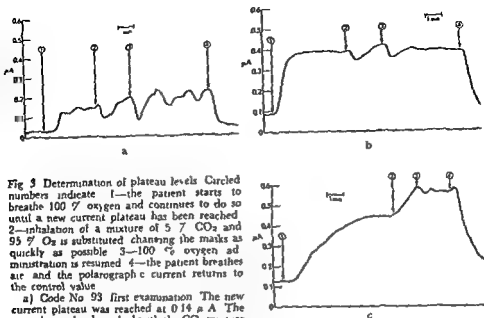


Fig 3 Determination of plateau levels. Circled numbers indicate 1—the patient starts to breathe 100 % oxygen and continues to do so until a new current plateau has been reached 2—inhalation of a mixture of 5 % CO_2 and 95 % O_2 is substituted changing the masks as quickly as possible 3—100 % oxygen administration is resumed 4—the patient breathes air and the polarographic current returns to the control value

a) Code No 93 first examination. The new current plateau was reached at $0.14 \mu\text{A}$. The new plateau level reached with the CO_2 mixture was $0.20 \mu\text{A}$. The rise after resuming oxygen breathing may represent a residual effect of the CO_2 . The curve demonstrates a CO_2 effect by the rapid increase in pO_2 from the plateau level during oxygen administration.

b) Code No 96 third examination. After radiation therapy the plateau levels of the polarographic current on air and oxygen breathing were higher than at the first examination. A brief administration of the 5 % CO_2 mixture (at 2) resulted in a slight increase in pO_2 from $0.38 \mu\text{A}$ to $0.41 \mu\text{A}$ which is not a significant change.

c) Code No 83 third examination. After administration of oxygen there was again a high plateau current ($0.44 \mu\text{A}$). An increase to $0.56 \mu\text{A}$ followed the period of breathing the 5 % CO_2 mixture. This is the maximal difference observed after radiation therapy and suggests a CO_2 effect.

quarters of an hour (colpophotography generally preceding the pO_2 measurements). The patients were very cooperative but not to tire them unnecessarily certain time limits were observed. Further we did not want the patients to experience any untoward effects of carbon dioxide breathing and therefore made them breathe the CO_2 mixture for only a few minutes at a time. This determined the sequence of gas breathing to be found in the examples of records and the tables of results. Concern for the patients precluded an ideal experimental set up.

Two parameters were compared: response time and plateau level.

Response time is the time (in seconds) from mask application to the first detectable deviation of the recorded polarographic current from the control value. The initial deflection from the control level was generally quite distinct and to ensure reproducible conditions the mask was always applied immediately prior

to inspiration. If the response to both O_2 and the $CO-O_2$ mixture was ill defined, the records were omitted from comparison. The response time thus represents the lung-uterus circulation time plus the intratumor circulation and diffusion time.

Plateau level represents the maximum increase in current following the first five to ten minutes of oxygen breathing.

All comparisons have been paired, meaning that each patient breathed both gases alternately during the same examination, under essentially the same conditions. The second response time was determined only after the control value of polarographic current, on room air, had been reached. For plateau levels, the masks with different gases were changed as quickly as possible to make the 'dip in pO_2 ' as small as possible. The sequence of events is illustrated in the examples of Figs 2 and 3.

Wilcoxon's test for pair differences was used, the probabilities relating to the two-tailed test (Documenta Geigy Scientific Tables 1962).

Results

Response time Comparisons of response time at the first, second and third examinations are shown in Tables 1, 2 and 3, respectively. No difference was found in any of the groups between the response time of the two gases. If all the response times are compared without relation to treatment, there is still no difference between the gases, suggesting that any small difference between the individual examinations most likely has been due to chance.

Plateau level Comparisons of the first and third examinations are shown in Tables 4 and 5. Before radiation treatment the tumor oxygen tension attained a higher plateau when the CO_2 mixture was administered to the patient than when pure oxygen was given.

The difference found for the first examination could not be confirmed for the third. It should be noted, however, that the plateau levels on oxygen found at the third examinations were generally much higher than those at the first.

In the comparisons of Tables 4 and 5, the CO_2 mixture was administered after the pure oxygen. In a number of patients, oxygen was administered a second time after the few minutes of the CO_2 mixture, with no difference observed in the plateau response.

Discussion

Our results indicate that the inhalation of a mixture of 5% CO_2 and 95% O_2 may result in slightly higher tumor oxygen tension in cervix cancer before radiation treatment than the inhalation of 100% O_2 at one atmosphere.

Tables 1 to 3

Comparison of response times at the 1st 2nd and 3rd examinations — Horizontally the response times are arranged in true examination order vertically the arrangement is according to Wilcoxon's test for paired comparisons — CO₂ indicates the 5% carbon dioxide mixture and O₂ the pure oxygen

Code number	Response time in seconds (in order of application)			Wilcoxon's test between CO ₂ first and O ₂ second	
	CO	O	CO	Diff	Rank number

Table 1 — First examination

50	9	9	—	0	
56	21	21	—	0	
43	15	17	—	2	1
B-a	12	9	—	3	
B-b	18	21	15	3	3
57	6	9	—	3	4
41	24	21	21	3	
53	45	39	—	6	
42	33	42	15	9	7
52	0	15	—	15	8

$$T = 13 \quad n = 8 \quad 2\alpha > 10$$

No difference

Table 2 — Second examination

38		51	33		
46	—	15	18		
39	15	15	—	0	
51	12	9	—	3	
43	18	12	12	6	1
44	10	12	—	6	2
40	21	10	10	6	3
52	14	0	—	11	4
				14	5

$$T_1 = 15 \quad n = 5 \quad 2\alpha = 10$$

Series too small for conclusion

Table 3 — Third examination

50	15	15			
39	24	24		0	
52	18	18		0	
42	27	30		0	
35	15	19		3	1
43	30	36		5	
40	18	12		6	3
48	3	9		6	
47	21	30		6	4
				9	5
					6

$$T = 6 \quad n = 6 \quad 2\alpha > 10$$

No difference

Tables 4 and 5

Comparisons of plateau levels — Arrangement as for tables 1 to 3

Code number	Baseline current (air breathing) $\mu A \times 100$	Plateau level $\mu A \times 100$		Plateau level increase over baseline in %		Wilcoxon's test	
		100% O ₂	5% CO ₂ 95% O ₂	100% O ₂	5% CO ₂ 95% O ₂	* Diff	Rank number

Table 4 — First examination

90	14	19	19	136	136	0	
105	10	18	17	180	170	10	1
94	3	23	22	760	733	38	25
111	3	4	5	133	166	33	25
110	5	13	15	260	300	40	4
104	1	3	4	300	400	100	5
101	1	11	13	1100	1300	200	6
103	1	25	27	2500	2700	200	7
93	3	14	20	467	667	200	8
96	1	13	17	1300	1700	400	9

$T_2 - 3.5 n = 9$
 $0.5 > 2\alpha = 0.9$
 Significant difference

Table 5 — Third examination (after irradiation)

84	20	44	43	220	215	5	1
83	7	11	12	157	172	15	2
89	8	16	18	267	300	33	3
96	9	38	41	422	456	34	4
87	20	67	76	335	380	45	5
86	13	39	32	300	246	54	6
88	11	22	15	200	136	64	7
90	14	36	45	257	322	65	8
94	11	54	45	491	409	82	9
85	13	44	56	338	432	94	10

$T_2 - 23 n = 10$
 $10 > 2\alpha = 10$
 No difference

pressure. Since the inspired gas contained 5% by volume less oxygen, the opposite effect could be expected if the hypercapnia was without effect. This effect of CO₂ on tumor oxygen tension could not be observed during radiation treatment. No difference was found in the response time between the two gases.

Carbon dioxide acts as a respiratory stimulant. The effect on the circulation

is complex. There is increased cardiac output. The direct effect on blood vessels is dilatation whereas the indirect effect is activation of the sympathetic nervous system. Peripherally local vasodilatation appears to be stronger than the nervous vasoconstriction (GOODMAN & GILMAN 1955). There is evidence that carbon dioxide also acts directly upon tumor vessels of transplantable mouse hepatomas (KLIGERMAN & HENEL 1961) but the response is unpredictable. Another factor to consider is that carbon dioxide produces a shift to the right in the oxyhemoglobin dissociation curve, the most important result probably being a better oxygen yield to the tissues.

These considerations suggest that CO might increase oxygen tension in peripheral tissues and possibly also in tumors. Increased tumor oxygen tension is also the most likely explanation of the better results of radiotherapy in animals reported by DuSAULT (1963) and by INCH, McCREDIE & KRUM (1966). The latter investigators noted an effect in poorly vascularized isomplants but not in well vascularized isotransplants.

Our results may be of some help in differentiating the mechanisms whereby hypercapnea might increase tumor oxygen. Since the measurement of lung tumor circulation time indicated by the response time, remains unchanged, increased cardiac output does not seem to be a significant mechanism. Peripheral vasodilatation might give a real increase in tissue oxygen tension or an apparent increase due to lessened distance from the measuring electrode to the capillary wall. An increase in the plateau reading of pO_2 with the CO mixture was observed only in the unirradiated cancers. This suggests that if the tumor vessels are already maximally dilated by the radiation effect similar to the radiation erythema of skin there will be no response to other vasodilating agents. The higher plateau level of tumor pO_2 on oxygen after radiation therapy would support this assumption. A similar rise in average pO_2 in tumor following external radiation therapy has been observed with the patient breathing air in a much larger series of cases (to be published elsewhere). Since the plateau reading is higher after radiation both with air and oxygen breathing a vasodilating effect of CO may be present but more difficult to demonstrate and possibly of less significance. A rise in pO_2 due to a shift in the oxyhemoglobin dissociation curve would not be expected to show any relation to radiation treatment and may be assumed to be of less importance.

Since the CO mixture was administered after O_2 a conditioning effect of pure O_2 cannot be ruled out. As previously stated oxygen was administered a second time after the few minutes of the CO mixture in several patients, with no difference observed in the plateau response. To really test this possibility however would have required more prolonged administration of the CO mixture before O_2 which was not done because of concern for the patients.

Tables 4 and 5

Comparisons of plateau levels — Arrangement as for tables 1 to 3

Code number	Baseline current (air breathing) $\mu A \times 100$	Plateau level $\mu A \times 100$		Plateau level increase over baseline in %		Wilcoxon's test	
		100% O ₂	5% CO ₂ 95% O ₂	100% O ₂	5% CO ₂ 95% O ₂	% Diff	Rank number

Table 4 — First examination

90	14	19	19	136	136	0	
105	10	18	17	180	170	10	1
94	3	23	22	766	733	38	2.5
111	3	4	5	133	166	33	2.5
110	5	13	15	260	300	40	4
104	1	3	4	300	400	100	5
101	1	11	13	1100	1300	200	6
103	1	25	27	2500	2700	200	7
93	3	14	20	467	667	200	8
91	1	13	17	1300	1700	400	9

$$T_1 = 3.5 \quad n = 9$$

$$0.5 > 2\alpha > 0.2$$

Significant difference

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94	11	54	45	491	409	82	9
85	13	44	56	338	432	94	10

$$T = 23 \quad n = 10 \quad 2\alpha = 10$$

No difference

pressure. Since the inspired gas contained 5 % by volume less oxygen, the opposite effect could be expected if the hypercapnea was without effect. This effect of CO₂ on tumor oxygen tension could not be observed during radiation treatment. No difference was found in the response time between the two gases.

Carbon dioxide acts as a respiratory stimulant. The effect on the circulation

REFERENCES

- DESCHNER E E and GRAY L H Influence of oxygen tension on X ray induced chromosomal damage in Ehrlich ascites tumor cells irradiated in vitro and in vivo Radiat Res 11 (1959) 115
- DOCUMENTA GEIGY SCIENTIFIC TABLES Geigy Basle 1967
- DU SALLT L A Effect of oxygen on the response of spontaneous tumours in mice to radiotherapy Brit J Radiol 36 (1963) 749
- GOODMAN L S and GILMAN A Pharmacological basis of therapeutics Third edition Macmillan New York 1965
- INCH W K McCREDIE J A and KRLUV J Effect of breathing 5 % carbon dioxide and 95 % oxygen at atmospheric pressure on tumour radiocurability Acta radiol Ther Phys Biol 4 (1966) 17
- KLIGERMAN M M and HEHEL D K Some aspects of microcirculation of a transplantable experimental tumor Radiology 76 (1961) 810
- KOLLER O Vascular patterns of the uterine cervix Scandinavian University Books Oslo 1963
- KOLSTAD P Vascularization oxygen tension and radiocurability in cancer of the cervix Scandinavian University Books Oslo 1964

Previous studies of cervix cancer have demonstrated that hypoxic foci are probably present (KOLSTAD 1964). Since the range of low pO_2 which causes reduced radiosensitivity but not cell death is very limited, any slight increase in tumor pO_2 may theoretically be of importance (DESCHNER & GRAY 1959). Whether this can be achieved by administration of 100 % O_2 at atmospheric pressure is presently being tested in a clinical trial at the Norwegian Radium Hospital. The present study suggests that a mixture of 5 % CO_2 and 95 % O_2 may give better tumor oxygenation than pure oxygen, if administered at the beginning of radiotherapy.

SUMMARY

Clinical tests were made in 37 patients with carcinoma of the uterine cervix to investigate the effect on tumor oxygen tension of a mixture containing 5 % CO_2 and 95 % O_2 as compared to the effect of 100 % O_2 inhaled at one atmosphere's pressure. Oxygen tension was measured polarographically in tumor tissue. Before the radiation treatment, the CO_2 mixture resulted in slightly higher maximum oxygen tension than the breathing of pure O_2 . After a series of fractionated external betatron treatments this difference had disappeared which would seem to indicate that the observed increase in tumor oxygen tension associated with the addition of CO_2 be due primarily to vasodilatation of tumor vessels.

ZUSAMMENFASSUNG

Klinische Versuche wurden an 37 Patientinnen mit Karzinom des Cervix uteri vorgenommen um die Wirkung am Sauerstoffdruck des Tumorgewebes von einer Mischung enthaltend 5 % CO_2 und 95 % O_2 im Vergleich mit der Wirkung von 100 % O_2 inhaliert beim Druck von 1 Atmosphäre zu untersuchen. Der Sauerstoffdruck wurde polarographisch im Tumorgewebe gemessen. Bevor der Bestrahlungstherapie bewirkte die CO_2 Mischung einen unbedeutend höheren maximalen Sauerstoffdruck als die Inhalation von reinem Sauerstoff. Nach einer Reihe von externen Betatronbestrahlungen verschwand dieser Unterschied was vermuten liess dass die mit der Zugabe von CO_2 beobachtete Zunahme im Tumor Sauerstoffdruck vor allem der Dilatation der Blutgefässe des Tumors zuzuschreiben sei.

RÉSUMÉ

Des tests cliniques ont été pratiqués sur 37 malades atteintes de cancer du col de l'utérus pour comparer les effets sur la tension d'oxygène de la tumeur d'un mélange contenant 5 % de CO_2 et 95 % d' O_2 et les effets de l'oxygène pur inhalé à la pression d'une atmosphère. La tension d'oxygène a été mesurée polarographiquement dans le tissu tumoral. Avant le traitement par les radiations le mélange contenant du CO_2 donnait des tensions maximales d'oxygène un peu supérieures à celles que donnait l'inhalation d'oxygène pur. Après une série de traitements externes fractionnés par le béta-tron cette différence disparut ce qui fait penser que l'augmentation de la tension d'oxygène de la tumeur liée à l'addition de CO_2 soit due essentiellement à la dilatation des vaisseaux de la tumeur.

inflammation as a result REEFER (1934) believed the lesions to be of the same type as in other granulomatous inflammatory conditions and to be caused by a protein complex, forming on reaction between tumour antigen and phospholipid rich antibodies

A fair proportion of the published cases of epithelioid cell granulomatosis in the region of malignant growths have been seen in patients irradiated for carcinoma of the uterine cervix Radiotherapy has often been related to the development of epithelioid cell granulomatosis because radiation certainly accelerates the destruction of the tumour tissue with consequent increase in the frequency of the lesions The most likely explanation for the relatively high frequency of cervical carcinoma in these series is perhaps that squamous epithelial growths are more prone to cause epithelioid cell granulomatosis than others

This investigation is a continuation of the work of GORTON & LIVELL in Lund upon epithelioid cell granulomatosis and was carried out to determine whether any variation in frequency occurred with age lymph node metastases or tumour stage or with the intensity and duration of the radiotherapy given

Material and Methods The material consisted of 145 patients with carcinoma of the uterine cervix examined between 1958 and 1964 and operated upon *ad modum* Wertheim with regional lymphadenectomy One hundred and thirty nine of these patients had squamous epithelial carcinoma and 6 had adenocarcinoma Four of the patients had not undergone radiotherapy

The patients mostly received preoperative roentgen therapy (four pelvic fields of 1 200 to 2 400 R per field) and intra uterovaginal radium treatment (three treatments at 10 day intervals with a total dose of 6 800 to 7 200 mg/hr for 3 to 4 weeks) The interval between termination of radiotherapy and operation was at least 2 months and seldom more than 3 months

Results

Eight of the 145 patients (5.5%) were found to have epithelioid cell granulomatosis of the regional lymph nodes Two of them had both epithelioid cell granulomatosis and metastases In none of these eight patients had preoperative roentgen examination revealed any obvious change Preoperative examination of seven of the patients had included serum electrophoresis The α_1 , α_2 and γ values were moderately increased in it including one patient with palpable axillary lymph nodes and one with palpable inguinal lymph nodes No biopsy specimens of these lesions were obtained Urography disclosed no signs of tuberculosis or other abnormalities in any of the eight patients

SARCOID-LIKE LESIONS (EPITHELIOID CELL GRANULOMATOSIS) OF REGIONAL LYMPH NODES IN ASSOCIATION WITH CARCINOMA OF THE CERVIX

by

BENKT HOGSTEDT

The occurrence of sarcoid like lesions in the regional lymph nodes in patients with various forms of malignant epithelial tumours was first described in the beginning of the 1950s (GHERARDI 1950, NADEL & ACKERMANN 1950, SYMMERS 1951 and GORTON 1953). Larger series have since been reported (GORTON & LINELL 1957 with 34 cases, WUKETICH 1959 with 29 cases, and HAGERSTRAND & LINELL 1964 with 14 autopsy cases). Thirty two cases in all have also been described by TEN SELDAM (1956), DONATI et coll (1961) and CHIECO BIANCHI (1963).

Epithelioid cell granulomatosis of the regional lymph nodes has also been seen in association with other types of neoplasms. Thus, GORTON & LINELL reported one case of sarcoma of the uterus and one of malignant melanoma and WUKETICH one case of seminoma.

According to most authors, the lesions should be distinguished from generalized sarcoidosis. The changes are believed to be due to a local reaction of the lymph nodes to disintegrating tumour tissue with granulomatous in

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that in the present series epithelioid cell granulomatosis was diagnosed only once between the years 1961 to 1964. Since sarcoid lesions are sometimes transient and may be related to radiotherapy the patients with epithelioid cell granulomatosis were studied for any difference from the rest of the series regarding the interval between the beginning of radiotherapy and the time of the operation. No such difference was however apparent and the interval did not vary from year to year either. The moderate variation of the duration of radiotherapy (see the table) may be explained by the somewhat longer treatment in stages II—IV.

The interval in the series of GORTON & LIVELL between termination of radiotherapy and the operation was usually 4 months compared with 2 to 3 months in the present series. This difference can however hardly explain the decrease during the years from 1961 to 1964 for the treatment was the same throughout the entire 1958—1964 period.

No differences with respect to age, stage of tumour or metastases to the lymph nodes could be found between patients with and respectively, without epithelioid cell granulomatosis.

SUMMARY

Eight out of a series of 145 women operated upon for carcinoma of the uterine cervix were found to have developed epithelioid cell granulomatosis of the regional lymph nodes.

ZUSAMMENFASSUNG

Es fand sich, dass in acht von 145 Frauen, die für Cervixkarzinom operiert worden waren, eine Epitheloidzellengranulomatose der Regionallymphdrüsen vorlag.

RÉSUMÉ

Sur une série de 145 femmes opérées pour cancer du col de l'utérus, huit présentaient une granulomatose à cellules épithélioïdes des ganglions lymphatiques de la région.

REFERENCES

- CINQUE-BIANCHI L. Study of 13 cases of cancer with associated sarcoidosis of the regional lymph nodes. *Tumori* 49 (1963) 429.
 DONATI L., STOFFELI F. and MASSELLI E. Anatomico-clinical data on regional lymphopathy associated with malignant neoplasm. *Boll. Soc. ital. Biol. sper.* 37 (1961) 159.
 GUERARDI G. J. Local lymph node sarcoidosis associated with ca. of the bile ducts. *Arch. Path.* 49 (1950) 163.

Table

Survey of the material — 145 patients with carcinoma of the uterine cervix examined between 1958 and 1964

Number of patients	With epithelioid granulomatosis	Mean age	Tumour stages				Spread to lymph nodes	Duration of preoperative radiotherapy in days		
			I	II	III	IV		Stage I	Stages II-IV	Total
1958	31	2	45.0	21	4	2	3	100	115	103
1959	23	4	43.5	13	10	0	4	105	111	108
1960	23	1	47.9	13	8	2	3	108	119	113
1961	23	0	42.7	12	9	2	3	104	118	111
1962	16	0	42.9	10	6	0	8	115	113	114
1963	12	0	51.4	8	4	0	4	126	139	130
1964	17	1	45.3	8	8	1	2	105	100	102
Total	145	8	45.2	89	49	7	27	106	115	110

Three of the patients with epithelioid cell granulomatosis have in the meantime died from recurrence of tumour and have been examined post mortem. The deaths occurred 2, 3 and 6 years after operation. No sarcoid lesions were evident in the organs examined histologically (lungs, heart, liver, spleen, kidneys, the suprarenal, hilar and parathyroid glands, and, in two of the patients, also the axillary and inguinal lymph nodes).

No epithelioid cell granulomatosis was present in patients with adenocarcinoma or in those who had not received radiotherapy. The patients have been classified in the table according to age, stage of disease, metastases to the lymph nodes and interval between termination of radiotherapy and operation.

Histologic findings The appearances resembled those of generalized sarcoidosis. Pale, swollen epithelioid cells in rounded foci, often with giant cells of the Langhans or foreign body type were present. The lymph nodes had signs suggesting more or less severe sinus catarrh with dilated sinuses, containing pale, swollen endothelial cells and a relatively small number of lymphocytes. Conditions transitional between sinus catarrh and well defined epithelioid cell granulomas with or without giant cells were sometimes present.

Discussion

Epithelioid cell granulomatosis was evident in 5.5 % of the patients and agrees well with the figure given by GORTON & LINELL (7.9 %) for a similar series collected during the 1948—1954 period. It seems remarkable however

DESTRUCTION OF THE HYPOPHYSIS WITH IMPLANTS OF PURE ^{90}Y METAL

by

GLUSTAF NOTTER OLOF MELANDER and LARS JOHANSSON

Destruction of the pituitary gland by implantation of isotopes is nowadays the usual technique for the elimination of hypophyseal hormonal activity. However, it is difficult to achieve complete cessation of the pituitary function due to the special topography of the hypophysis and its high radioresistance in relation to that of the surrounding tissues.

A radiation dose of 70 000 to 100 000 rad delivered in 10 to 14 days is required to produce necrosis in normal pituitary tissue (Rasmussen et coll 1953, NOTTER 1959). When applying these doses, sufficient protection of the surrounding tissues can be obtained only by using pure β emitters such as ^{90}Y and ^{106}Ru .

Two types of complications may develop after interstitial irradiation of the hypophysis: damage to the cranial nerves and cerebrospinal rhinorrhoea. The first may be avoided by exact implantation of the isotopes but the second is unpredictable and is caused by radiation injury to the diaphragma sellae and the anterior wall of the sella. We therefore have tried to diminish the trauma in the latter by decreasing the diameter of the implants from 1.0 to 0.5 mm. The yttrium oxide cylinders of this dimension became too fragile however and we therefore employed the pure yttrium metal which is harder

- GORTON G Post irradiative prophylactic extraperitoneal lymphadenectomy in carcinoma of the uterine cervix Acta radiol (1953) Suppl No 100
- and LINELL F Malignant tumours and sarcoid reactions in regional lymph nodes Acta radiol 47 (1957) 381
- HAGERSTRAND I and LINELL F The prevalence of sarcoidosis in the autopsy material from a Swedish town Third international Conference on sarcoidosis Reprint Acta med scand 176 (1964) Suppl 425
- NADEL E M and ACKERMANN L V Lesions resembling Boeck's sarcoid in lymph nodes draining an area containing malignant neoplasm Amer J clin Path 20 (1950) 952
- REFVEM O The pathogenesis of Boeck's disease Acta med scand (1954) Suppl 294
- SYMERS W St C Localized tuberculoid granulomas associated with carcinoma Their relationship to sarcoidosis Amer J Path 27 (1951), 493
- TRN SELDAM M R Sarcoid like reactions in lymph nodes draining carcinoma Med J Aust 43 (1956) 916
- WUETICH E On the epithelioid cellular tuberculoid reactions in the lymph nodes in malignant tumors Frankfurt Z Path 70 (1959) 187



Lateral roentgenograms of the sella (a) immediately after implantation of four ^{90}Y metal cylinders in the hypophysis and (b) 14 days after the implantation when partial disintegration of the metal cylinders had occurred. After injection into the sella of paraffin wax containing gold powder for treatment of cerebrospinal rhinorrhea the mixture could be seen as a thin layer on the anterior surface of the hypophysis and in the sella wall (c).

implants. Impurities of about 0.01 % tantalum and less than 0.001 % terbium were also present in the metal.

By activation analysis of the metal cylinders the γ activity peaks were identified as those of ^{140}Th (half life 73 days), of ^{140}Dy (half life 2.3 hours) and of ^{140}Ta (half life 115 days).

By delaying the implantation until 40 hours after the activation of the implants, the dose contribution from the ^{140}Dy activity was completely avoided. The radiation dose from ^{140}Th is negligible. The additional radiation dose from ^{140}Ta can be diminished by using a high neutron flux and a short irradiation time. The rods were therefore irradiated for about 1.5 hours in a neutron flux of 1.8×10^{14} neutrons/cm²/second.

The dose increase from the ^{140}Ta contamination at 1 cm distance from the periphery of the partially disintegrated cylinder may reach about 3 rad during the first 14 days after implantation and about 30 rad after complete decay. This is roughly of the same magnitude as the Bremsstrahlung from the ^{90}Y (NOTTER 1959), and is thus of no practical importance.

Although negligible in relation to the total radiation dose the ^{140}Ta contamination has to be taken into account for a long time as an additional background source when determining radioiodine uptake in the thyroid after implantation.

Discussion

The degree of pituitary destruction is related to the accuracy of isotope positioning in the gland. However, after implanting ^{90}Y metal, the dose distribution changes in a non-predictable and uncontrolled manner by the varying disintegration and spread of the cylinder within the pituitary gland, making

These metal cylinders partly disintegrated in contact with blood and interstitial fluid, however, and this increased the radiation dose to the periphery of the gland and facilitated total destruction but also caused difficulties in dosimetry. Since this behaviour of yttrium metal in human tissue was unexpected we felt justified in publishing our observation.

Material and Methods Yttrium metal has been implanted since March 1961 in 19 patients according to the technique described by NOTTER (1959). Fifteen of the patients had advanced breast cancer, one acromegaly, and three patients had juvenile diabetes mellitus with vascular complications. As a rule 6 mm long and 0.5 mm thick cylinders were inserted bilaterally 3 to 4 mm from the midline. If the sella was longer than 10 mm, two cylinders 4 mm long were implanted on each side (see accompanying figure). The activity of the implants varied between 2 and 3 mCi. After implantation, roentgenograms of the sella were obtained every third day for three weeks. Any possible leakage and contamination of the surrounding tissues were checked. Blood and cerebrospinal fluid of three patients were examined spectrometrically and counted with a $2\frac{1}{2} \times 3$ NaI (T1) well type scintillation counter.

Results

Complete loss of pituitary hormonal activity was achieved in 14 of the 19 patients by implantation of ^{90}Y metal cylinders into the hypophysis. This included disappearance of the urinary excretion of gonadotrophins, a radioiodine uptake in the thyroid of under 15 %, low PBI values and development of cortisone deficiency 10 to 12 days after the implantation.

In the first two patients of this series, the defects in the anterior wall of the sella were blocked by titanium screws, using the technique of FORREST et coll (1958), no screws were inserted in the subsequent patients. Cerebrospinal rhinorrhoea developed in five of the latter but ceased spontaneously in two of them. Two other patients were treated by intrasellar injection of paraffin wax, and this stopped the leakage (see illustration).

Roentgenograms obtained after implantation indicated that the cylinders disintegrated to various degrees, probably depending on their contact with blood and fluid in the tissues. Spectrometric determination and scintillation measurements in samples of blood and cerebrospinal fluid from three patients taken 1 to 20 days after implantation, revealed no evidence of leakage or contamination by ^{90}Y outside the hypophysis.

Spectrography and photospectrometry of the yttrium metal used in this series disclosed impurities of 0.04 % dysprosium compared with 0.0017 % in the highly purified Y_2O_3 powder generally used for preparation of the

RÉSUMÉ

Dix neuf malades atteints de cancer du sein avancé d'acromégalie ou de diabète sucré juvénile avec complications vasculaires ont été traités par implantation bilatérale dans l'hypophyse de cylindres d'yttrium métal ayant chacun une activité de 2 à 3 mCi. L'activité hormonale de l'hypophyse a été complètement supprimée chez 14 de ces malades. Les examens spectrométrique et les mesures de radioactivité n'ont pas montré de contamination des tissus environnants du sang ni du liquide céphalo-rachidien par l'yttrium 90 .

REFERENCES

- FORREST A, BLAIR D and VALENTINE J. Screw implantation of the pituitary with yttrium 90 . *Lancet* II (1958) 197.
- HAYEN M et JURET H. Prophylaxie des fistules consécutives aux implantations d'yttrium intrahypophysaire par mise en place d'un écran paraffiné dans la selle turcique. *Presse méd* 70 (1962) 1587.
- HOLMER A, BARRING N, MELANDER O, NOTTER G und WIDELL C. Strontium 90 Applikator für interstitielle Bestrahlung der Hypophyse. *Fortschr Röntgenstr* 106 (1967) 574.
- NOTTER G. A technique for destruction of the hypophysis using Y^{90} spheres. *Acta radiol* (1959) Suppl No 184.
- MELANDER O und NORBERG E. Elektrisch geheizte Kanüle zur intrasellären Paraffinimplantation nach interstitieller Bestrahlung der Hypophyse. *Acta radiol Ther Phys Biol* 6 (1967) 491.
- RASMUSSEN T, HARPER P and KENNEDY TH. The use of beta ray point source for destruction of the hypophysis. *Surgical Forum* 4 (1953) 681.
- TALAIRACH J, ABOLKER J, TOURNOUX P et DAVID M. Technique stéréotaxique de la chirurgie hypophysaire par voie nasale. *Neurochirurgie* 2 (1956) 3.

exact dosimetry impossible. Radioactivity measurements of cerebrospinal fluid and blood have not shown contamination outside the hypophysis, and careful studies of the patients in this series have not given evidence of radiation damage of the cranial nerves after bilateral implantation of 2 to 3 mCi ^{90}Y cylinders.

Contrary to our expectations, the incidence of cerebrospinal leakage was not diminished by causing less trauma of the front wall of the sella by way of decreasing the diameter of the implant to 0.5 mm. Leakage developed in five of the 19 patients. This complication was treated by intrasellar injection of paraffin according to the suggestion of HAYEM & JURET (1962). We are using a mixture of paraffin wax and either Au or Y_2O_3 powder to make it visible in fluoroscopy. This mixture is injected through a specially manufactured, electrically heated, cannula, permitting slow injection of small amounts of the paraffin wax mixture (0.5 ml) into the sella (NOTTER et coll. 1967). This technique was used in two patients with cerebrospinal leakage and in both patients the leakage ceased (see the accompanying figure). The paraffin wax mixture is now injected prophylactically in all patients after implantation and has proved effective.

The screw implantation technique suggested by TALAIRACH et coll. (1956) and FORREST et coll. (1958) is no longer used in our department. It diminished the frequency of rhinorrhoea but failed to afford total protection from it. Bone resorption around the screw frequently caused it to drop out of the sella wall and thus led to late cerebrospinal rhinorrhoea.

During the last year we have preferred to irradiate the pituitary gland by insertion of a ^{90}Sr needle applicator which seems preferable for several reasons (HOLMER et coll. 1967).

SUMMARY

Nineteen patients with advanced mammary carcinoma, acromegaly, or juvenile diabetes mellitus with vascular complications were treated by bilateral pituitary implantation of yttrium metal cylinders each of an activity of 2 to 3 mCi. Complete loss of pituitary hormonal activity was achieved in 14 of the patients. No contamination of the surrounding tissues, blood or cerebrospinal fluid with ^{90}Y could be observed by spectrometric studies or radioactivity measurements.

ZUSAMMENFASSUNG

Neunzehn Patienten mit fortgeschrittenem Brustkrebs, Akromegalie oder juveniler Diabetes mellitus mit Gefäßveränderungen wurden mit bilateraler Implantation von 2 bis 3 mCi Yttrium Metallzylindern behandelt. Bei 14 dieser Patienten ging die hypophysäre Hormonausscheidung vollständig verloren. Keine Kontamination des umgebenden Gewebes, des Blutes oder der Zerebrospinalflüssigkeit mit ^{90}Y konnte bei spektrographischen Studien oder Radioaktivitätsmessungen festgestellt werden.

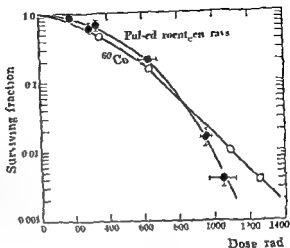


Fig. 1 Survival curves for cultured human kidney cells exposed to ^{60}Co gamma rays at 150 ± 10 rad/min (open circles) and pulsed 10 MV roentgen rays with the total dose being delivered in 3×10^{-8} seconds (solid circles) both under aerated conditions

Material and Methods The human kidney cells line T1 originally obtained from BARENDSEN used in these experiments were serially propagated in Eagle's Minimum essential medium and 10% fetal bovine serum. We irradiated six to eight hour single cell cultures growing in 35 mm plastic petri dishes on day old feeder layers of 5×10^4 irradiated (4000 rad) cells per 35 mm dish.

We used 10 MV roentgen rays generated from a Physics International pulsed electron accelerator in the dose rate range of 10^4 to 10^{13} rad/min. Each total dose was delivered in a single pulse of 3×10^{-8} seconds duration. For comparison we used ^{60}Co gamma rays at a dose rate of 150 ± 10 rad/min. For both radiations the dose delivered to each group of exposed cultures was determined by LiF thermoluminescence, a method found to be dose rate independent in the range used. Dosimetry capsules and cultures were simultaneously exposed to each dose. Both radiations were filtered by one inch of polyethylene.

The petri dishes containing the cells to be irradiated were mounted in a mylar film faced aluminum exposure wheel (Tonn 1966). The medium was removed from the petri dishes just prior to irradiation and the dishes were exposed vertically so that they were perpendicular to the incident radiation beams. In those experiments in which oxygen was removed, high purity nitrogen was passed over the cultures for 20 min prior to exposure. Subsequent to exposure the medium was replaced and the cultures were incubated at 37°C and fed with fresh medium every 5 days until visible colonies developed (~ 2 weeks). Surviving fractions were determined on the basis of colony counts in exposed and control cultures.

PULSED HIGH-INTENSITY ROENTGEN RAYS

Inactivation of human cells cultured in vitro and limitations on usefulness in radiotherapy

by

PAUL LODD, H. SAUL WINCHELL, JOSE M. FIORE and GARY L. JONES

The suggestion that neoplastic cells are frequently more hypoxic than their normal counterparts, in conjunction with the observation that hypoxic mammalian cells are partially protected from effects of ionizing radiation (DEWEY 1960), has stimulated efforts to seek radiation, the action of which is independent of the presence of oxygen. Some decrease in the oxygen effect with the use of high intensity electron beams has been observed in chemical systems (ROTHLAT & SUTTON 1960), and in bacteria (DEWEY & BOAC 1959), and with high intensity proton beams in water (SHALEK & BONNER 1953). Decreased incidence of chromosome breakage at high radiation dose rates has also been reported (KIRBY SMITH & DOLPHIN 1958).

If the reduced oxygen effects noted in these experiments with high intensity radiations are to be applicable in clinical radiotherapy, such effects must be present within the appropriate dose range for human treatment. In addition, therapeutic applicability requires the use of radiation with adequate penetration. The recent availability of linear accelerators for the production of high energy, high intensity photons suggested experiments to determine the dose dependency of radiation induced inhibition of colony formation by cultured human cells under aerated and anoxic conditions. Our experimental results define the limitations of such high intensity radiation in human radiotherapy.

eliminating the oxygen effect. If the mechanism whereby high intensity reduces the oxygen effect is the use up of available intracellular oxygen at a rate greater than the diffusion of available oxygen into the irradiated volume then the minimum dose rate (10^6 rad/s) obtained by SHALEK & BONNER) is a measure of the rate of oxygen diffusion into the irradiated volume.

DEWEY & BOAG, using dose rates in excess of 10^6 rad/s (actually about 10^{10} rad/s) found that doses greater than 13 000 rad were adequate for eliminating the effect of 1% oxygen in nitrogen in irradiated cultures of the bacterium *Serratia marcescens*. If we take the value of 13 000 rad as representing the minimum dose required for the use up of intracellular oxygen at this partial pressure (about 7.6 mm Hg), then one would anticipate a required dose of 260 000 rad ($20 \times 13\,000$) to use up the intracellular oxygen at atmospheric pressure (about 152 mm Hg). Recently FPP, WEISS & FENLON (1967) determined that the threshold for oxygen use up in bacterial strain *E. coli* B/r in air is about 60 000 rad.

It is therefore not surprising that the experiments we describe in this work did not demonstrate a reduced oxygen effect under aerated conditions at dose rates of 10^{11} to 10^3 rad/s and in the dose range of 200 to 1 050 rad.

On the basis of the quantitative considerations just presented an estimation may be made of the required partial pressure of oxygen in tissue to allow complete oxygen use up by therapeutically usable radiation doses. If we assume 2 000 rad to be the largest single acceptable therapeutic dose then a high intensity radiation pulse (delivered at more than 10^6 rad/s) of this magnitude would require that the oxygen partial pressure in the irradiated tissue be less than 1.1 mm Hg to insure use up of the residual oxygen with resultant elimination of the oxygen effect. Therefore, in order to utilize in radiotherapy the diminished oxygen effect seen in high intensity radiation experiments it would be necessary to reduce the partial pressure of oxygen in the target area tissue to about 1.1 mm Hg for the duration of the radiation pulse. Such a procedure is limited by considerations of the human physiologic effects of temporary extreme hypoxia.

Acknowledgements

We are greatly indebted to Mrs C. L. Boerke and Mrs W. M. Jackson for unstinting laboratory assistance and to Mr B. Bernstein and the staff of Physics International, San Leandro, California, for performing the irradiations and dosimetry and for their generous sharing of their facilities and equipment. This work was supported by NASA and AEC.

SUMMARY

Pulsed 10 kV roentgen rays administered at dose rates of 10^{11} to 10^{12} rad/s and in the total dose range of 200 to 1 050 rad/pulse did not differ significantly from ^{60}Co gamma rays in their ability to inactivate aerated cultured human cells. It is estimated that a total dose

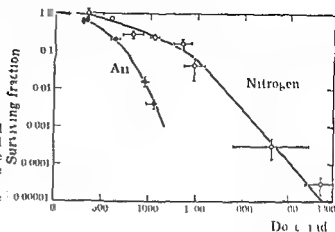


Fig 2 Survival curves for cultured human kidney cells exposed to pulsed 10 MV roentgen rays. The air curve is the one shown in fig 1 and the nitrogen curve differs in that purified nitrogen was passed over the cells for 20 minutes prior to irradiation.

Results

Survival curves for cells exposed to pulsed roentgen rays and ^{60}Co gamma rays under aerated conditions are presented in Fig 1. Vertical error bars represent the standard errors of mean survival propagated from the relative errors of the mean colony counts on control and irradiated plates. Horizontal error bars represent standard deviations of doses determined by the multiple (9 or more) LiI dosimeters used in measuring the dose at each individual dose point. The dose rate in rad/s at each dose of pulsed roentgen rays was different and was equivalent to the dose at that point divided by 3×10^{-8} seconds. The highest dose rate represented in this graph is approximately 3×10^{11} rad/s. The two curves of Fig 1 do not differ significantly considering the experimental conditions.

The survival curve for cells exposed to pulsed roentgen rays while in a nitrogen atmosphere is presented in Fig 2 and compared with that obtained under aerated conditions. The results suggest that fully anoxic conditions were not achieved in the experiment, since the ratio of doses in nitrogen to those in air required for equivalent survival is less than that anticipated under complete anoxia. However, it can be concluded that the effect of oxygen at atmospheric pressure did not disappear at these radiation intensities.

Discussion

SHALEK & BONNER, using hydrogen peroxide formation in pure water as their end point at total proton doses in excess of 10^7 rad, found that the difference between yields in air saturated water and helium saturated water disappeared at dose rates greater than 10^8 rad/s. These published observations suggest that all ionization produced at intensities greater than 10^8 rad/s is equally effective in

PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF ^{90}Sr IN MICE

Development of carcinomas in the mucous membranes of the head

by

AGNAR NILSSON

Much work has been done on ^{90}Sr induced neoplasms but it seems that the attention has been mainly concentrated on the induction of osteosarcomas in the skeleton for a study of the histogenesis and development of such lesions and their possible dose dependency (ANDERSON, ZANDER & KUZMA 1956 FINKEL 1959 LITVAEL & BISH 1959 FINKEL BERGSTRAND & BISH 1961 KOWALEWSKI & RODIN 1964, NILSSON 1962 LITVINOV 1963 OWEN SIMONS & VAUGHAN 1957 and others). With respect to skeletal malignancies the problem of dose relationships has not yet been unambiguously solved and even less is known concerning neoplasms deriving from other tissues such as hematopoietic organs and mucous membranes in close contact with bone.

A comprehensive study has been made in mice on dose relationships and the pathologic effects and carcinogenic influence of varied doses of ^{90}Sr , in particular on the skeleton the hematopoietic tissues and the mucous membranes of the head. The results of these investigations will be reported in separate papers the present

of 260 000 rad delivered at dose rates greater than 10^8 rad/s is necessary to eliminate the oxygen effect in aerated cells and that at dose rates greater than 10^8 rad/s the partial pressure of oxygen in tissue would have to be reduced to less than about 11 mm Hg prior to irradiation to eliminate the oxygen effect

ZUSAMMENFASSUNG

Pulsierende 10 MV Röntgenstrahlen bei Dosisverhältnissen von 10^{11} bis 10^7 rad/s und bei Dosen von 200 bis 1 050 rad/Puls waren nicht signifikant verschieden von ^{60}Co Gammastrahlen für die Inaktivierung von Menschenzellen in aerobischer Kultur. Es wurde berechnet, dass man um den Sauerstoffeffekt bei Dosisverhältnissen grösser als 10^8 rad/s zu beseitigen mindestens 260 000 rad benötigt. Für die Beseitigung des Sauerstoffeffekts bei Dosisverhältnissen grösser als 10^8 rad/s muss der Sauerstoffdruck weniger als 11 mm Hg sein.

RÉSUMÉ

Les rayons de roentgen pulvés de 10 MV administrés avec un débit de dose de 10^{11} à 10^7 rad/s et à des doses totales allant de 200 à 1 050 rad/impulsion ne présentent pas de différence significative avec les rayons gamma du ^{60}Co en ce qui concerne l'inactivation de cellules humaines en cultures aérées. Les auteurs estiment qu'il faut une dose totale de 260 000 rad administrés avec un débit supérieur à 10^8 rad/s pour supprimer l'effet oxygène dans les cellules aérées et que pour des débits de dose supérieurs à 10^8 rad/s il faudrait réduire la pression partielle d'oxygène dans le tissu à moins de 11 mm de Hg environ avant l'irradiation pour éliminer l'effet oxygène.

REFERENCES

- BARENDSEN G W, BEUSKER I L J, VERGROESEN A J and BUDDE L. Effects of different ionizing radiations on human cells in tissue culture. II Biological experiments. *Radiat Res* 13 (1960) 841.
- DEWEY D L. Effect of oxygen and nitric oxide on the radiosensitivity of human cells in tissue culture. *Nature* 186 (1960) 780.
- and BOAG J W. Modification of the oxygen effect when bacteria are given large pulses of radiation. *Nature* 183 (1959) 1450.
- ENGLE H. Amino acid metabolism in mammalian cell cultures. *Science* 130 (1954) 437.
- EPP E R, WEISS H and TENLON A. Observations of the oxygen effect and radiation recovery in bacterial cells irradiated with high intensity pulsed electrons. *Radiation Res* 31 (1967) 646.
- KIRBY SMITH J S and DOLPHIN G W. Chromosome breakage at high radiation dose rates. *Nature* 182 (1958) 270.
- ROTHBLAT J and SUTTON H C. The effects of high dose rate of ionizing radiations on solutions of iron and cerium salts. *Proc roy Soc A* 253 (1960) 490.
- SHALEK R J and BONNER T W. Formation of hydrogen peroxide in water by 1 MeV protons. *Nature* 172 (1953) 259.
- TODD P W. Reversible and irreversible effects of densely ionizing radiations upon the reproductive capacity of cultured human cells. *Med Coll Virginia Quart* 1 (1966) 2.

PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF ^{90}Sr IN MICE

Development of carcinomas in the mucous membranes of the head

by

AGNAR NILSSON

Much work has been done on ^{90}Sr induced neoplasms but it seems that the attention has been mainly concentrated on the induction of osteosarcomas in the skeleton for a study of the histogenesis and development of such lesions and their possible dose dependency (ANDERSON, ZANDER & KUUMA 1956 FINKEL 1959 FINKEL & BISKIS 1959 FINKEL BERGSTRAND & BISKIS 1961 KOWALEWSKI & RODIN 1964 NILSSON 1962 LITVINOV 1963 OWEN, SISSONS & VAUGHAN 1957 and others). With respect to skeletal malignancies the problem of dose relationships has not yet been unambiguously solved, and even less is known concerning neoplasms deriving from other tissues such as hematopoietic organs and mucous membranes in close contact with bone.

A comprehensive study has been made in mice on dose relationships and the pathologic effects and carcinogenic influence of varied doses of ^{90}Sr in particular on the skeleton the hematopoietic tissues and the mucous membranes of the head. The results of these investigations will be reported in separate papers the present

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of 260 000 rad delivered at dose rates greater than 10^9 rad/s is necessary to eliminate the oxygen effect in aerated cells and that at dose rates greater than 10^8 rad/s the partial pressure of oxygen in tissue would have to be reduced to less than about 11 mm Hg prior to irradiation to eliminate the oxygen effect

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REFERENCES

- BARENDSEN G W, BRUSKIN I L J, VERHOEVEN A J and BUDKE I. Effects of different ionizing radiations on human cells in tissue culture. II Biological experiments. *Radiat Res* 13 (1960) 841.
- DEWEY D L. Effect of oxygen and nitric oxide on the radiosensitivity of human cells in tissue culture. *Nature* 186 (1960) 780.
- and BOAG J W. Modification of the oxygen effect when bacteria are given large pulses of radiation. *Nature* 183 (1959) 1150.
- FAGLE H. Amino acid metabolism in mammalian cell cultures. *Science* 130 (1954) 432.
- EPP F R, WEISS H and FINLON A. Observations of the oxygen effect and radiation recovery in bacterial cells irradiated with high intensity pulsed electrons. *Radiation Res* 31 (1967) 646.
- KIRBY SMITH J S and DOLPHIN G W. Chromosome breakage at high radiation dose rates. *Nature* 182 (1958) 270.
- ROTHBLAT J and SUTTON H C. The effects of high dose rate of ionizing radiations on solutions of iron and cerium salts. *Proc Roy Soc A* 253 (1960) 490.
- SHALEK R J and BONNER I W. Formation of hydrogen peroxide in water by 1 MeV protons. *Nature* 172 (1953) 259.
- TODD P W. Reversible and irreversible effects of densely ionizing radiations upon the reproductive capacity of cultured human cells. *Med Coll Virginia Quart* 1 (1966) 2.



Fig. 1 Hard palate. Normal mucous membrane from a 22-day-old male mouse (van Gieson $\times 980$)

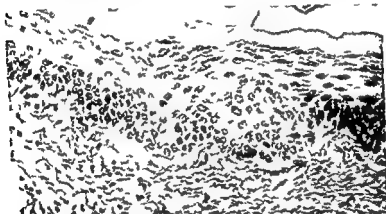


Fig. 2 Hard palate. Mucous membrane with dysplasia and increased mitotic activity from a mouse killed 150 days after treatment with 0.8 μCi ^{90}Sr /g bodyweight (van Gieson $\times 280$)

same room. In all the series the mice were housed in groups of ten animals per cage throughout the whole experiment.

The nomenclature used is in accordance with the general principles in human pathology.

Results

Tumour development The earliest morphologically detectable signs of disturbance of the mucous membranes of the ^{90}Sr treated animals consisted of enhanced mitotic activity, mostly in the stratum germinativum of the epidermis as com-

Table 1

Experimental conditions and doses employed

Dose of Sr in $\mu\text{Ci/g}$ body weight	Total number of mice	Number of mice killed in groups of 5 every month	Duration of experiment in days	Number of animals dead before sacrifice
1.6	120*	65	300	50
0.8	121	75	360	46
0.4	122	95	480	27
0.2	120**	100	540	17
Control	95	94***	570	1

* Out of these animals five were lost during the experiment

** Out of these animals three were lost during the experiment

*** Only four animals were sacrificed in the last test group

dealing mainly with carcinomas in the mucous membranes of the head. Many of the mice with these carcinomas had osteosarcomas as well, or leukemia, or both. Reports concerning carcinomas are sparse (FINKEL 1959, NILSSON 1962, VAUGHAN 1962) and it has been the aim of this investigation to obtain more precise information on latency time, frequency and sites, histogenesis, development and dose relationships.

Material and Methods Four groups of CBA mice, 75 days old, were treated intraperitoneally with $^{90}\text{Sr}(\text{NO}_3)_2$. In addition, a group of 95 animals without ^{90}Sr treatment were used as controls for a study of the natural incidence of tumours. At intervals of 7, 14, 21, and 30 days after injection of ^{90}Sr , and then at monthly intervals, five mice from each group were selected at random and sacrificed, until all mice in each series had been utilized. The experimental conditions and the ^{90}Sr doses employed are recorded in Table 1.

It was not possible to keep the number of killed mice in each dose group the same, because with increasing doses the survival times became much shorter. However, both the sacrificed mice and the mice dead before sacrifice have been investigated, though handled separately.

The mice were decapitated. The head was divided in the median plane during dissection, fixed in Stieve's fluid and decalcified in 20% formic acid for histologic examination. Conventional methods were used, the sections being stained according to the van Gieson method, with Ehrlich's haematoxylin-eosin, and Lillie's azur-eosinate. The animals were fed during the experiment on a standard diet *ad libitum* and kept under similar environmental conditions in the



Fig 1 Hard palate Normal mucous membrane from a 72 day old male mouse (van Gieson $\times 280$)



Fig 2 Hard palate Mucous membrane with dysplasia and increased mitotic activity from a mouse killed 150 days after treatment with $0.8 \mu\text{Ci } ^{90}\text{Sr/g}$ bodyweight (van Gieson $\times 280$)

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Fig 3 Hard palate Mucous membrane with increasing degree of hyperplasia and dysplasia with disarranged slightly atypical basal cells from a mouse 300 days after injection of $0.8 \mu\text{Ci } ^{32}\text{Sr/g}$ bodyweight van Cieson $\times 280$

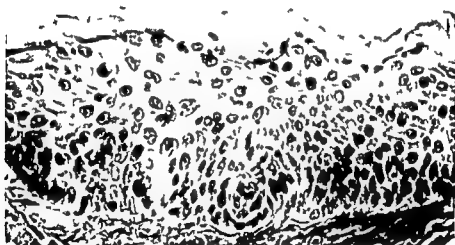


Fig 4 Hard palate Mucous membrane with markedly dysplastic changes and predominantly slightly atypical basal cells extending into the stratum spinosum from a mouse 360 days after injection of $0.8 \mu\text{Ci } ^{32}\text{Sr/g}$ body weight van Cieson $\times 280$

pared to the normal mucous membranes and there was furthermore usually a tendency towards concentration of the mitotic activity to circumscript areas. Slight disarrangement, and often a changed polarity and slightly increased size of the basal cells could be observed. These usually focally situated changes became

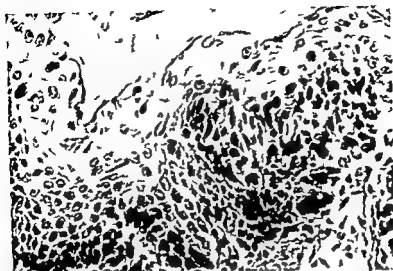


Fig 5 Hard palate Mucous membrane with marked dysplasia and scattered moderately atypical nuclei situated in different layers of the epidermis from a mouse 40 days after injection of $1.6 \mu\text{Ci } ^{90}\text{Sr}$ 5/g bodyweight van Gieson $\times 280$



Fig 6 Hard palate Mucous membrane with carcinoma in situ from a mouse 120 days after injection of $1.6 \mu\text{Ci } ^{90}\text{Sr}$ 5/g bodyweight van Gieson $\times 290$

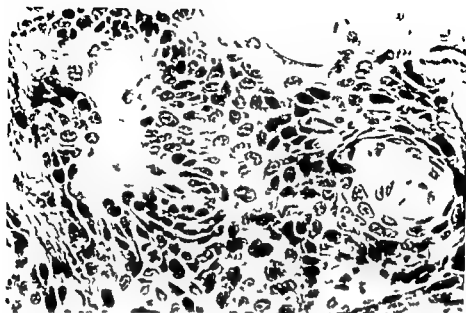


Fig 7 Oral mucous membrane with a highly differentiated squamous carcinoma from a mouse 270 days after injection of $1.6 \mu\text{Ci } ^{90}\text{Sr/g}$ body weight via Cieson $\times 280$

successively more accentuated. The basal cell layer was broken up and cell buds or scattered cell elements from this layer began to extend into the stratum spinosum. The basal cells were usually hyperplastic with hyperchromatic and slightly atypical nuclei. Changes of the now mentioned types have in this investigation been termed *dysplasia with slight atypism* (Figs 2 to 4).

In local foci there was a continuously increasing number of more atypical basal cells extending into all the layers of the epidermis. Giant nuclei also began to appear. In some cases, premature keratinization was evidenced by cells containing eosinophilic homogenous droplets of intracellular keratin. The destruction of the normal histologic structures was extensive. This stage has in the present communication been termed *dysplasia with moderate atypism* (Fig 5).

In the next stage the cells were of definitely carcinomatous type, and all layers of the epidermis were infiltrated by these. A distinction has, however, been made between *carcinoma in situ* (Fig 6) and *invasive cancer* (Fig 7). The first type is represented by local carcinomatous noduli of limited extent, not infiltrating surrounding tissue or the basal membrane.

The epithelium of the tongue of the same animal has been used as an unirradiated histologic control. Since the average ranges of the β particles from ^{90}Sr and its ^{90}Y daughter in soft tissues are respectively, 0.3 and 2.1 mm, this mucosa

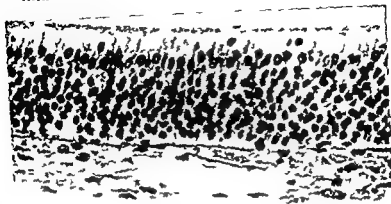


Fig 8 Region olfactory nasal mucous membrane from a 28-day old mouse van Gieson $\times 400$

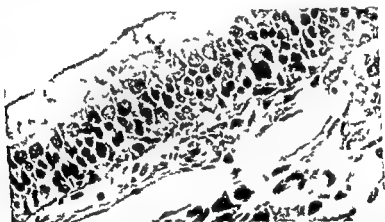


Fig 9 Region olfactory nasal mucous membrane from a mouse 270 days after injection of $16 \mu\text{Ci Sr/g}$ body weight. Depletion of nervous olfactory cells marked sustentacular cells mitotic figure along the basal membrane van Gieson $\times 450$

may be regarded as unirradiated in comparison with parts of the oral mucosa irradiated from underlying bone structures

Tumours formed in the cutaneous membranes of the nose follow the same pattern of development as the oral carcinomas. In some cases tumour formation has however also been observed in the olfactory membranes. The most important early observation was a reduction and a later disappearance of the nervous olfactory cells swelling of the sustentacular cells and the appearance of mitotic

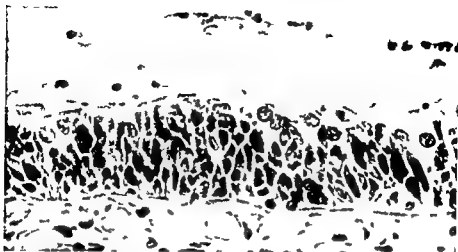


Fig 10 Regio olfactoria Mucous membrane from a mouse 300 days after injection of 16 μCi $^{90}\text{Sr/g}$ bodyweight Most of the olfactory nerve cells have disappeared abundance of atypical cells and mitotic figures van Gieson $\times 450$

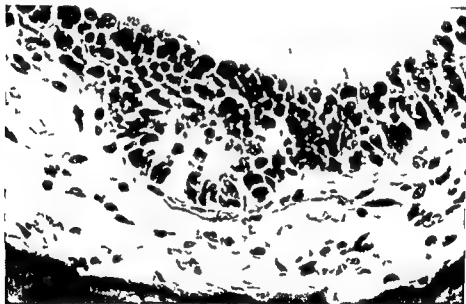


Fig 11 Regio olfactoria Mucous membrane from a mouse 240 days after injection of 16 μCi $^{90}\text{Sr/g}$ bodyweight Bud of atypical cells showing a focal expansion of the basal membrane into underlying connective tissue van Gieson $\times 450$

figures along the basal membrane The cells replacing the nervous elements were usually elongated, hypertrophic and with strongly hyperchromatic nuclei which seemed to invade the mucosa from the basal membrane It seemed to be basal cells that comprised the greater bulk of these cells (Figs 11 to 12)

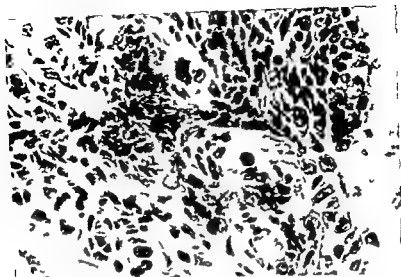


Fig. 17. Nalcaity invasive carcinoma in a mouse 300 days after injection of $1.6 \mu\text{Ci}$ ^{90}Sr /g bodyweight van Gieson $\times 430$

The changes successively leading to the development of carcinoma follow nearly the same pattern in the different dose groups. They commence earlier however and develop more rapidly with increasing ^{90}Sr doses. This is exemplified in Fig. 13 representing the results obtained from each group of animals sacrificed at 30 day intervals. Only in the highest dose group have carcinomas of the olfactory mucous membrane been detected.

Tumour frequency. The number of tumours occurring in the different dose groups are recorded in Table 2 and in Fig. 14 the accumulated total number of tumours are represented in relation to the time elapsed after the ^{90}Sr administration.

A total of 80 carcinomas and carcinomas in situ were found in the whole experiment when the sacrificed mice and the animals dead before sacrifice were counted together. Of these 56 or 70 % were found in the $1.6 \mu\text{Ci}$ group, 21 or 26 % in the $0.8 \mu\text{Ci}$ group and only 3 or 4 % in the $0.4 \mu\text{Ci}$ series. It should be pointed out that the number of tumours obtained is a minimum since no serial sectionings were performed.

Latency time. A comparison of the various time intervals between injection of ^{90}Sr and the occurrence of dysplastic changes, carcinomas in situ and carcinomas has been made for the different dose groups in Table 3.

Table 2
Tumour frequency in the different dose groups

Dose $\mu\text{Ci } ^{90}\text{Sr/g}$ body weight	Number of mice in vestigated	Number of sacrificed mice	Number of tumour bearing mice	Total num ber of tumours	Number of tumours per mouse	Percent mice with tumours
1.6	115	65	38	56	0.49	33.0
0.8	121	75	17	21	0.17	14.0
0.4	122	93	3	3	0.02	2.5
0.2	117	100	0	0	0.00	0.0
Control	95	91	0	0	0.00	0.0

Table 3

Comparison of latency time in the development of dysplastic changes and carcinomas in mucous membranes in the different ^{90}Sr dose groups

Dose $\mu\text{Ci } ^{90}\text{Sr/g}$ body weight	Dysplasia		Carcinoma in situ + carcinoma			
	Sacrificed animals		Sacrificed animals		Mice dead before sacrifice	
	Number	Days Mean \pm SE	Number	Days Mean \pm SE	Number	Days Mean \pm SE
1.6	17	152 \pm 19.0	10	242 \pm 11.2	20	232 \pm 3.9
0.8	17	249 \pm 15.6	11	330 \pm 8.1	6	319 \pm 8.4
0.4	23	335 \pm 16.6	2	465	1	407
0.2	7	497 \pm 24.4	0	—	0	—

Table 4

Percentual tumour distribution at different sites

Group	Hard palate	Incisious part		Nose
		Upper jaw	Lower jaw	
Whole experiment	38.8	11.3	13.8	16.3
1.6 μCi group	60.7	10.7	12.5	16.1
0.8 μCi group	61.9	9.5	9.5	19.0
0.4 μCi group		1.3	2.6	

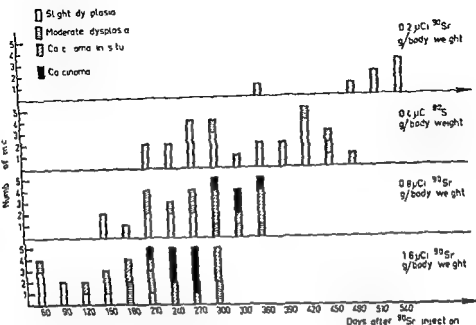


Fig. 13 Histograms showing start and development of changes leading to carcinomas. The mice were killed in groups of five at 30-day intervals.

Tumour sites The sites of the carcinomas and carcinomas in situ are shown in Table 4. Out of the total of 80 tumours 47 or 58.8% were located in the mucous membranes lining the palatine bone. The most frequent site was in a limited area adjacent to the termination of the hard palate. No tumours were situated in the soft palate and only few in the rugae area of the hard palate. In an area lining the incisive part of the mandible 11 tumours or 13.8% were detected and in the opposite region of the upper jaw 9 or 11.3% were found. Of 13 tumours or 16.3% in the nasal cavities three were situated in the olfactory region and the remainder in the cutaneous part of the nose.

Tumour type All the carcinomas investigated, excepting those in the olfactory region, have been of the squamous type. The degree of differentiation varied, however. Of 31 tumours in the 1.6 μCi group twenty-two were highly differentiated squamous carcinomas, five were moderate and four were low differentiated. Of the 9 tumours in the 0.8 μCi group the corresponding figures were four, four and one. The carcinomas defined as highly differentiated were strongly keratin producing, the moderate type slightly, and the low differentiated tumours did not show any evidence of keratin formation.

Discussion

The results of this investigation seem to bear in evidence that the squamous cell carcinomas in the cutaneous membranes of the mouth and nose start at local sites in the stratum germinativum. It is possibly basal cell elements, damaged by the irradiation from the underlying bone, which initiate the changes ultimately leading to overt neoplasia.

With respect to the mucous membrane from the olfactory region of the nose it also seems possible to assume from the few cases investigated that the lesion started from basally situated cells of epidermal origin. In the evaluation of the relationship between these changes and irradiation, the localization of the tumours is of the greatest importance. As may be seen from Table 4, most of these tumours emanated from the mucous membrane of the hard palate. They were usually formed in small foci in an area between the rugous part and the termination of the hard palate. They could also be found around the incisious part of the upper and lower jaw. Histologically, this may be explained by the fact that in these parts the contact between the mucous membranes and the underlying bone structures is very intimate.

In contrast to these observations, no carcinomas were detected in the epithelium of the tongue. It is also obvious from Table 4 that the dose inside a range between 1.6 and 0.8 μCi of $^{90}\text{Sr/g}$ bodyweight has little influence on tumour localization. Exceptions are carcinomas in the olfactory membranes, which have been detected only in the 1.6 μCi group.

A comparison of the latency time for development of dysplastic changes as well as carcinomas *in situ* and carcinomas also seems to indicate dose dependency. Thus, dysplastic changes started on an average 90 days earlier in the 1.6 than in the 0.8 μCi group. This time relationship still exists if the latter series is compared with the 0.4 μCi group. Between the 0.2 and 0.4 μCi groups this time interval was however increased to 162 days (see Table 3). A possible explanation is that the development of dysplastic changes may be delayed for a considerable time by an intact recovery mechanism. Also for the carcinomas, the latency time was still approximately 90 days shorter for the 1.6 μCi group as compared to the 0.8 μCi group. Between the latter and the 0.4 μCi group, the time interval increased to 135 days. It may be pointed out that only carcinomas *in situ* developed in the 0.4 μCi group. If the mice in this group had been allowed to survive for a longer period it seems probable that more tumours would have had time to develop. On the other hand, animals given the 0.4 μCi dose seemed to have a greater ability to resist cellular transformations ultimately leading to tumour.

Not only the site of the earliest changes and the latency time for tumour

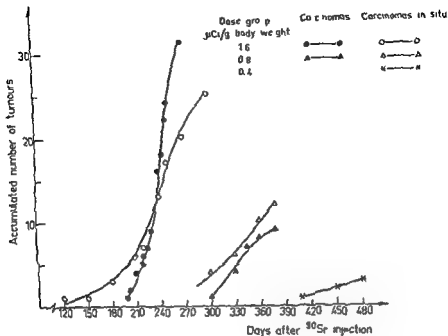


Fig 14 Accumulation of total number of tumours obtained in the different dose groups

development but also the carcinoma frequency and the total number of tumours obtained seem to indicate a dose relationship (Table 2 Fig 14). Thus there is approximately twice as high values for tumour bearing mice, total number of tumours and percent mice with tumours in the 16 μCi as compared to the 0.8 μCi group. On the other hand this correlation does not exist between the 0.8 and 0.4 μCi groups but this could possibly be explained by the fact that the mice had not survived long enough to give time for maximum tumour development in the lowest dose group.

SUMMARY

Radiostrontium induced carcinomas of the mucous membranes of the head have been studied in mice. Four groups were injected with respectively 16 0.8 0.4 and 0.2 μCi ^{90}Sr per gram bodyweight. The development of carcinoma usually started in the stratum germinativum of the epidermis usually at local sites the most common being the mucous

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MOBERGER G Personal communication

NILSSON A ^{90}Sr induced osteosarcomas *Acta vet scand* 3 (1962) 185

— Influence of gestation and lactation on radiostrontium induced malignancies in mice

I Incidence distribution and characteristics of ^{90}Sr induced malignancies *Acta radiol Ther Phys Biol* 6 (1967) 33

OWEN M SIMONS H A and VAUGHAN J The effect of a single injection of high dose of ^{90}Sr (500—1 000 $\mu\text{C/kg}$) in rabbits *Brit J Cancer* 11 (1957) 229

VAUGHAN J Cited from DOUGHERTY

membrane covering the palatine bone. A dose dependency seems to exist since with increasing doses of ^{90}Sr the latency time was shortened and the tumour frequency augmented.

ZUSAMMENFASSUNG

Radiostrontium induzierte Karzinome der Schleimhaut des Kopfes wurden in Mäusen studiert. Vier Gruppen wurden je mit 1,6, 0,8, 0,4 und 0,2 μCi ^{90}Sr per Gramm Körpergewicht intraperitoneal injiziert. Die Karzinom-Entwicklung fand erst in dem Stratum germinativum der Epidermis statt, meistens innerhalb begrenzter Regionen, häufigst in der Schleimhaut, die das Gaumenbein bedeckt. Eine Dosisabhängigkeit scheint zu bestehen, da mit erhöhten Dosen von ^{90}Sr die Latenzzeit verkürzt wurde und die Tumorfrequenz gesteigert wurde.

RESUME

L'auteur a étudié les cancers des muqueuses de la tête induits par le strontium radioactif. Quatre groupes de souris ont reçu une injection intraperitoneale de 1,6, 0,8, 0,4 et 0,2 μCi de ^{90}Sr par gramme de poids corporel respectivement. Les cancers ont commencé à se développer dans la couche germinative de l'épiderme habituellement en certains sièges dont le plus fréquent a été la muqueuse qui recouvre le palais. Ces cancers semblent dépendre de la dose puisque le temps de latence est raccourci et la fréquence des tumeurs augmente avec des doses croissantes de ^{90}Sr .

REFERENCES

- ANDERSON W. A. D., ZANDER G. and KUZMA J. F.: Carcinogenic effects of ^{45}Ca and ^{90}Sr on bones of CFI mice. *Arch. Path.* 62 (1956) 262.
- DOUGHERTY T. F.: Some aspects of internal irradiation. *Proceedings of a Symposium* p. 352. Pergamon Press, Oxford, 1962.
- FINKEL M. P.: Late effects of internally deposited radioisotopes in laboratory animals. *Radiat. Res.* (1959) Suppl. No. 1, p. 265.
- and BISKIS B. O.: The induction of malignant bone tumors in mice by radioisotopes. *Univ. Int. Cancer Acta* 15 (1959) 99.
- , BERGSTRAND P. J. and BISKIS B. O.: The latent period, incidence and growth of ^{90}Sr induced osteosarcomas in CFI and CBA mice. *Radiology* 77 (1961) 269.
- KOWALEWSKI K. and RODIN A. E.: Strontium 89 induced bone tumor in the rat. *Canad. J. Surg.* 7 (1964) 204.
- LITVINOV N. N.: Dynamics of the formation and development of bone sarcomas after damage by radioactive strontium and yttrium. US Atomic Energy Commission Translation Series AEC tr 3077. *Vop. Onkol.* 3 (1963) 285.

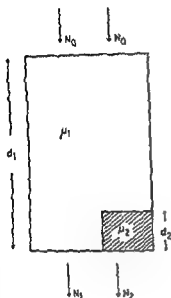


Fig. 1 Diagram illustrating a radiographed object with thickness d_1 containing a volume thickness d_2 with a different mass and/or chemical composition.

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Theoretical considerations

Assume an object (Fig. 1) with thickness d_1 irradiated by N_0 photons per unit area. μ_1 is the linear attenuation coefficient and N_1 the number of photons transmitted through the object per unit area. If the object contains a volume with thickness (d_2) having the linear attenuation coefficient μ_2 , the number of transmitted photons per unit area is N_2 . Then, with narrow beam geometry and monoenergetic radiation, the following equations will hold for the attenuation of the radiation:

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DETERMINATION OF SMALL MASS DIFFERENCES IN ROENTGENOGRAPHY

I Theoretical considerations

by

GUNNAR LÄSFL, BENGT K A MÅRTENSSON and KARL ÅKE OMNELL

Many pathologic conditions are accompanied by a local change in the mass and/or chemical composition of the body tissues involved. Roentgen examination is a most important tool for the detection and the interpretation of such conditions.

The differential blackening of the roentgen film is a function not only of mass differences within the object and/or differences in its chemical composition but also of several other factors such as the characteristics of the photographic emulsion (and intensifying screens), exposure data and the dark room procedure. From a diagnostic standpoint it is of importance to gain as much information as possible from the roentgenograms, i.e. to be able to demonstrate as small pathologic mass differences or differences in chemistry as possible. When a roentgenogram is evaluated visually, the signal from the image depicting the pathologic change is dependent not only on the texture of this image but also on distractions or 'noise' from adjacent areas in the roentgeno

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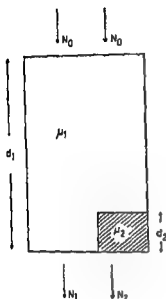


Fig. 1 Diagram illustrating a radiographed object with thickness d_1 containing a volume thickness d_2 with a different mass and/or chemical composition.

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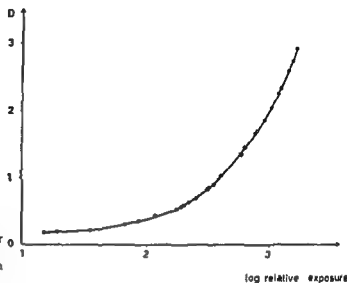


Fig. 2 The characteristic curve for Kodak periapical radiatized dental X-ray film exposed to roentgen radiation

The ratio between the number of transmitted photons will be

$$\frac{N_2}{N_1} = e^{(\mu_1 - \mu_2) d} \quad (1)$$

In roentgendiagnostic work, photographic film is mostly used as a detector for the radiation. The characteristic curve (Fig. 2) of the roentgen film gives the photographic density (D) as a function of the logarithm of the exposure (I).

At any point, D_1 , of the curve we define a function

$$\gamma_{D_1}(D) = \frac{D - D_1}{\log I - \log I_1} \quad (2)$$

where D is a variable point of the curve

From eq. (2) we obtain

$$\frac{1}{I_1} = 10^{\gamma_{D_1}(D)} \frac{D - D_1}{D} \quad (3)$$

For monoenergetic radiation and narrow beam geometry the exposure is directly proportional to the number of photons per unit area. Then, from eqs. (1) and (3) we obtain

$$10^{\gamma_{D_1}(D_2)} = e^{(\mu_1 - \mu_2) d}$$

$$d_1 = \frac{(D_2 - D_1) \ln 10}{\gamma_{D_1}(D_2) (\mu_1 - \mu_2)} \quad (4)$$

and hence

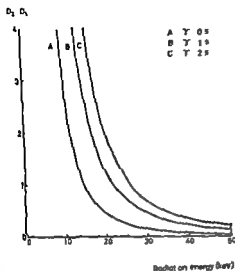


Fig. 3 Differences in photographic density as functions of the photon energies in keV at three values of γ . Calculation according to eq. (4) ($d = 1$ cm).

Thus a photometric evaluation of D_2 and D_1 makes it possible to quantitatively determine d according to eq. (4) provided the characteristic film curve, the radiation energy and the linear attenuation coefficient are known. Eq. (4) shows that a volume with thickness d_2 contained in an object with thickness d_1 will influence the difference in photographic density ($D_2 - D_1$), giving higher differences in photographic density with increasing values of γ , D_1 and $(\mu_1 - \mu_2)$.

At densities below a certain D value, which has to be determined experimentally, $\log D$ as a function of $\log \lambda$ will approximately be a straight line. The corresponding analytical approximation (NILSSON 1963) is

$$\lambda = B g Q D^{1/\alpha} \quad (5)$$

where λ is the exposure, B is a constant corresponding to a given radiation quality, g is a function (probably a constant) depending on the dark room procedure, Q is a constant for a given film type, D is the photographic density when the fog and base density has been subtracted and α is a constant. For given experimental conditions, eq. (5) can be written

$$D = k \lambda \quad (6)$$

where k is a constant. If in eq. (2) the difference $\log \lambda - \log \gamma_1$ tends to zero, $\gamma_{D_1}(D)$ will express the rate of change of D as a function of $\log \gamma$.

After differentiation of eq (6) we obtain

$$\frac{d(\ln D)}{d(\ln \gamma)} = \alpha \text{ but}$$

$$\frac{d(\ln D)}{dD} = \frac{1}{D}$$

After substitution, eq (7) can be written

$$\gamma_{D_1}(D) = \frac{dD}{d(\ln D)} \frac{d(\ln D)}{d(\ln \gamma)} \frac{1}{\log e} = D \alpha \frac{1}{\log e} \quad (8)$$

Provided the difference $(D_2 - D_1)$ is sufficiently small, substitution for $\gamma_{D_1}(D)$ in eq (4) gives

$$d_2 = \frac{D_2 - D_1}{\alpha D (\mu_1 - \mu_2)} \quad (9)$$

Discussion

For the sake of simplicity, in the theoretical considerations presented, a thickness difference in the object has been represented by a difference in mass and/or a difference in chemical composition. Accordingly, linear attenuation coefficients have been used instead of mass attenuation coefficients.

The relation between a thickness difference in a radiographed object, and the corresponding difference in photographic density of the roentgen film, is deduced from eqs (4) and (9).

While eq (4) is valid for all types of roentgen film and for the entire characteristic film curve before the solarisation, eq (9) holds at least for direct exposure films and for the range of photographic densities in which eq (5) may be applied. Another condition for application of eq (9) is that the thickness and photographic density differences have to be small enough to allow differential calculations. Consequently, since it is difficult to employ γ determinations with precision at small density differences, eq (9) offers the advantage that γ determinations do not have to be involved. On the contrary, in experimental determination of α must be performed. However, since α , following eq (6), is the inclination of the straight line representing the characteristic curve in a log log diagram, it is easy to evaluate.

According to eq (4), if the thickness difference is given, the corresponding difference in photographic density will increase with increasing γ value and with decreasing energy. This holds if absorption edges will not cause $(\mu_1 - \mu_2)$ to decrease with decreasing energy. In Fig 3, the result of a calculation at

three different γ values of thickness differences of aluminium in air is presented. At 30 keV the difference in photographic density, corresponding to a thickness difference of 0.1 cm at $\gamma = 0.5$ will be one third of that at $\gamma = 1.5$. These two $\gamma_D(D)$ values will be found at $D = 0.2$ and $D = 0.8$, respectively, for the characteristic curve in Fig. 2 giving an exposure ratio of about 1.45. Thus in the example given a three fold increase in difference in photographic density will be obtained at the cost of a more than four fold exposure. That is to say a three fold increase in detectability will be obtained with a more than four fold exposure.

Eqs (4) and (9) are valid for monoenergetic photons and narrow beam geometry. However, in roentgen diagnostics one has to utilize polyenergetic roentgen radiation. Provided the effect of the thickness difference on the spectral distribution of the roentgen radiation can be neglected eqs (4) and (9) are valid also for polyenergetic radiation. Then the difference between the linear attenuation coefficients $(\mu_1 - \mu_2)$ according to eqs (4) and (9) has to be substituted by the corresponding difference $\overline{\mu_1 - \mu_2}$

$$\text{where } \overline{\mu_1 - \mu_2} = \frac{1}{N} \int_0^{\infty} (\mu_1 - \mu_2) \lambda(h\nu) d(h\nu)$$

where N is the total number of photons of the spectrum and $\lambda(h\nu)$ is the number of photons with energies between $h\nu$ and $h\nu + d(h\nu)$.

In roentgendagnostic work it is impossible to prevent all scattered radiation from reaching the film emulsion. Consequently eqs (4) and (9) have to be corrected for the photographic density created by the scattered radiation. Such corrections are in a complicated manner dependent both on the spectral distribution of the radiation and the radiation geometry. Accordingly the influence of scattered radiation on eqs (4) and (9) has to be studied experimentally.

Eqs (4) and (9) give the important quantitative relationship between a thickness difference in a radiographed object and the corresponding difference in photographic density of the roentgen image. In order to optimize the roentgendagnostic procedure when small mass differences are examined the influence of such factors as radiation geometry, exposure time and radiation dose has to be studied experimentally utilizing eqs (4) and (9) as a basis.

SUMMARY

The relation between a thickness difference in a radiographed object and the corresponding difference in photographic density in the roentgenogram varies with the physical parameters involved. A theoretical treatment of this problem is presented.

ZUSAMMENFASSUNG

Die Beziehung zwischen dem Unterschied in der Dicke eines bestrahlten Objekts und dem entsprechenden Unterschied in der photographischen Schwarzung variiert mit Variationen in den physikalischen Parametern. Eine theoretische Behandlung dieses Problems wird vorgelegt.

RÉSUMÉ

La relation entre une différence d'épaisseur dans un objet radiographié et la différence de densité photographique correspondante varie quand varient les paramètres physiques concernés. Ce travail a pour objet une étude théorique de ce problème.

REFERENCE

NILSSON R. γ dose measurements with the Dupont 508 film in mixed radiation fields. AB Atomenergi Studsvik. Internal report RFA 487, 1963.

COMMERCIAL PHOTODIODES AS GAMMA AND ROENTGEN RAY DOSIMETERS

by

P. E. ÅSARD and G. BAARSEN

There has always been a need in radiotherapy to check the doses given to patients. The development in radiotherapy and radiophysics has led to more accurate estimates of doses partly because of the use of external beam treatment with high energy photons which facilitates dose calculations compared to conventional roentgen ray treatments and partly because of the fact that dose planning is now being more widely used. Individual dose planning does not however in all cases permit a sufficiently accurate determination of the dose at different points during the treatment of a patient. It is therefore highly desirable to be able to measure the dose directly. The necessity for measurement is particularly obvious when the thorax region has to be irradiated and when it is required to know the dose to the rectum and bladder for application of radium or similar sources in the vagina and uterus.

An important requirement for a radiation detector intended for use in *in vivo* measurements is that its dimensions be as small as possible. Sieverts Bg-chambers (0.5 cm in diameter and 2 cm long) are used at Radiumhemmet for measurements in the esophagus and rectum and a Siemens Gammameter with a CdS crystal is used for measurement of dose rates in gynecologic treat-

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ments with radium. In the last years, however, new dosimeters have been introduced which seem suitable for these purposes. These are of the solid state type, the thermoluminescence detector, and the p-n junction detector. The p-n junction detector has the advantage over the LiF dosimeter that the dose rate during treatment can be read directly on an instrument. The measuring equipment for the p-n junction detector can in most cases be an ordinary DC voltmeter and no bias voltage is needed. This eliminates the risk of electrical shock to the patient if the isolation should become damaged. The advantages over the ionization chamber is the higher sensitivity per volume, the robustness, and the fast response.

Details of investigations on commercial photodiodes and silicon solar cells have been published (MOODY et al. 1958, CALKINGS 1962, GULDBRANSEN & MADSEN 1962, WHELFTON & WATSON 1963 and JONES 1963). These results have stimulated us to investigate some other diodes in order to estimate their usefulness in clinical dosimetry. The silicon diodes tested were Siemens BPY 11 and BPY 100, and two Hoffmann solar cells, type B 120 CG 9 and N 120 CG 9, the latter described as radiation resistant by the manufacturers. The parameters investigated were (1) sensitivity, (2) exposure rate dependence, (3) temperature dependence, (4) energy dependence, and (5) radiation damage.

Function of the diode The solid state diode consists of a p and n layer separated by a depletion layer. This depletion layer is produced when the holes diffuse to the n layer and the electrons to the p layer, causing a voltage drop between the two layers. If a bias voltage is applied with positive polarity to the n layer and negative to the p layer, the depletion layer is increased. The sensitive part of the diode for ionizing radiation is the depletion layer and a small region around it determined by the diffusing length for the minority carriers. Charged particles produced by Compton, photo and Auger processes interact with the diode by exciting electrons up to the conducting band from the valence band, and corresponding holes are produced in the valence band. The charges produced in the sensitive region of the diode drift under the influence of the electric field in the depletion region producing a current through the diode.

No bias voltage is needed because the radiation produced holes are driven to the p layer and the electrons to the n layer, generating a photo voltage biasing the diode in the forward direction. If the diode is connected to an instrument with a load resistance R_L , part of the current goes through the instrument in reverse direction, and the other part leaks through the diode in a forward direction. If $R_L \rightarrow 0$, the whole current goes through the instrument, and if $R_L \rightarrow \infty$, the instrument measures the open circuit voltage.

SCHARF & SPARROW (1964) have calculated the photovoltaic current,

produced by roentgen rays in a p n junction, by methods similar to those applied for calculation of the photoresponse of a junction to visible light In current notation, the function of a diode can be described as follows

If I is the photovoltaic output current I_0 the current generated by the radiation and I_f the junction leakage current flowing in the forward direction then

$$I = I_0 - I_f \quad (1)$$

and I_f is proportional to the exposure rate An approximate equation for I_f is

$$I_f = I_0 [e^{qV/kT} - 1] \quad (2)$$

I_0 being the diode saturation current in reverse direction q the electronic charge V the forward voltage between cell terminals under closed circuit conditions k the Boltzmann constant and T the absolute temperature

If equations (1) and (2) are combined one obtains

$$I = \frac{kT}{q} \ln \left[\frac{I_0 - I}{I_0} + 1 \right]$$

When the load resistance $R_L \rightarrow \infty$ (i.e. $I \rightarrow 0$) V will be the open circuit voltage which is not proportional to the exposure rate and is temperature dependent The open circuit voltage is however approximately linear to the exposure rate when $\frac{qV}{kT} \ll 1$ (i.e. $V \ll 25$ mV at room temperature) Linearity of the photovoltage with exposure rate is also obtained when the leakage current $I_f = 0$ i.e. when $R_L \rightarrow 0$ (i.e. $I \rightarrow 0$) In that case

$$I = IR_L = I_0 R_L$$

is measured under short circuit conditions

Measuring techniques Maximum sensitivity is achieved if pulse counting is used but this requires a more complicated instrumental set up than simple DC-measurements of the current or voltage and it cannot be used at high dose rates The simplest method is to measure the open circuit voltage and this is also a more sensitive method than measuring the short circuit current Disadvantages are the temperature dependence and the non linearity with dose rate At small intensities however the open circuit voltage is approximately proportional to the exposure rate as pointed out above

Current measurements can also be made with reverse bias applied to the diode but JONES (1963) found that the ratio of the signal to the leakage current decreased with increased bias -

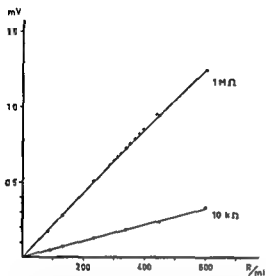


Fig. 1 Exposure rate dependence of a BPY 11 diode irradiated with a ^{60}Co beam at different load resistances. The signal for the 1 M Ω curve must be multiplied by 10.

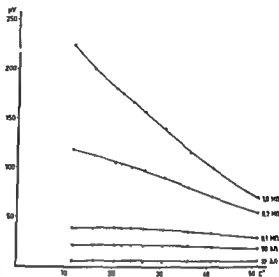


Fig. 2 Temperature dependence of a BPY 11 diode at different load resistances.

The dimensions of our BPY 11 and BPY 100 diodes are $4.8 \text{ mm} \times 2.2 \text{ mm} \times 0.9 \text{ mm}$, when used for measurements in water phantoms and for energy dependence measurements they were coated with epoxy resin and painted black. The Hoffman diodes are $10 \text{ mm} \times 4 \text{ mm} \times 0.5 \text{ mm}$. A Hewlett Packard DC microvoltmeter (425A) has been used in all the measurements.

Exposure rate dependence The voltage from a BPY 11 diode irradiated with ^{60}Co gamma radiation was measured at different exposure rates and load-resistances between 10 k Ω and 1 M Ω . As may be seen from Fig. 1, non-linearity is present at exposure rates higher than about 200 R/min at 1 M Ω in load resistance. This means that if the diode is used for a roentgen beam with a HVL of say 0.1 mm Cu, the deviation from a linear relationship between exposure rate and voltage is seen already at about 35 R/min as a result of the energy dependence of the diode. At 10 k Ω in load resistance the curve is linear, at least to the highest exposure rate measured ($\sim 600 \text{ R/min}$).

Temperature dependence In order to measure the temperature dependence, the diodes (BPY 11) were immersed in a water bath in which the temperature could be controlled to $\pm 0.5^\circ \text{C}$. The diodes were irradiated with ^{60}Co gamma radiation with an exposure rate of about 10 R/min. The temperature range was 10° to 50°C , and the load resistance was varied between 1 M Ω and 10 k Ω .

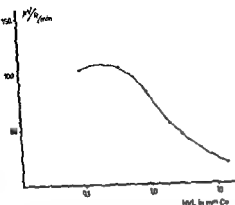


Fig 3 Energy dependence of a BPY 11 diode for ^{60}Co irradiation. The different HVL values correspond to 100 kV 1 mm Al, 140 kV 4 mm Al, 175 kV 0.5 mm Cu + 1 mm Al, 200 kV 0.4 mm Sn + 1 mm Al, 230 kV 1 mm Al + 0.6 mm Sn.

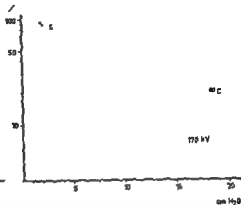


Fig 4 Depth doses measured with an ionization chamber (x) and a BPY 11 diode (O) for a ^{60}Co beam (SSD 60 cm) and a 170 kV roentgen beam with Thoreaus filter (FSD 40 cm). The curves are normalized to 5 cm depth. $A = 10 \text{ cm} \times 10 \text{ cm}$.

As will be seen from Fig 2 the sensitivity of the diode decreases with the temperature at high load resistances but becomes independent of temperature when the load resistance is $10 \text{ k}\Omega$ i.e. when the short circuit current is measured. Of the four diodes investigated one showed a similar response to the diode as in Fig 2 but the other two showed a slow increase up to about 26°C and then a decrease in response. The latter two diodes were independent of temperature at $100 \text{ k}\Omega$ due to differences in junction resistance as compared to the first diode.

Energy dependence The measurements were made free in air with a BPY 11 diode and the exposure was measured with a Victoreen chamber of known energy dependence. The load resistance for the diode was $1 \text{ M}\Omega$. The dose rate in all the measurements was kept so low that the signal from the diode was always less than 1 mV , thus in order to eliminate any faults depending on non linearity. The temperature was controlled to $\pm 1^\circ \text{C}$. In Fig 3 the sensitivity of the diode is plotted as a function of HVL. The diode is about 6 times (5-7) more sensitive when irradiated with a beam with HVL 0.1 mm Cu than when irradiated with ^{60}Co . WHELFORD & WATSON (1963) changed the energy response of their probe by making suitable filters which caused the curve representing the energy range between roentgen radiation with HVL 1 mm Cu and ^{60}Co gamma radiation to appear practically flat.

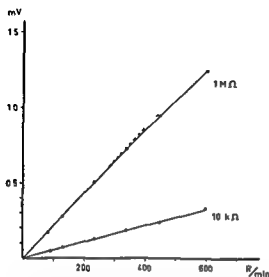


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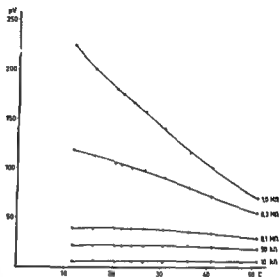


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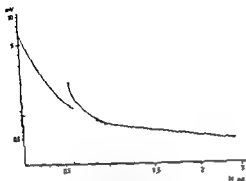


Fig 5 Radiation damage effect at Co irradiation measured for a BPY 100 diode No 4

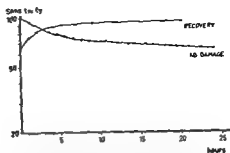


Fig 6 Loss of sensitivity as a function of the irradiation time for a Hoffmann solar cell N 120 CG 9 and the recovery as a function of the time after finishing the irradiation

Sensitivity and radiation damage The initial sensitivity of the various diodes are shown in a Table. The diodes were irradiated with a ^{60}Co beam with an exposure rate of 320 R/min. It is well known that when the energy of the secondary electrons is sufficient (>250 keV) they can produce interstitial vacancy pairs (Frenkel defects) and other changes in the silicon and thus change the sensitivity of the diode. These defects can produce donor and acceptor energy levels within the energy gap. The effect is however more complex than that (DEARNALEY 1964). Several investigations on these effects in p-n junctions have been reported (WHELFTON & WATSON 1963; ROSENZWEIG 1962).

To investigate the radiation damage effect for ^{60}Co radiation 5 BPY 11 diodes and 5 BPY 100 diodes were mounted on a perspex plate and irradiated simultaneously at 320 R/min. In the Table the D_{50} doses obtained are indicated, i.e. the doses which reduce the sensitivity to 50% of the initial sensitivity. The irradiations were performed in two sessions and the signals were measured with a load resistance of 1 M Ω . The diodes were irradiated in the first session for 28 hours and after an interval of 96 hours they were irradiated again for 47.5 hours.

An example of the curve for one of the diodes is given in Fig 5. As will be seen from the figure, the sensitivity of the diode increased during the period without irradiation. In all the ten figures obtained it was obvious that the curve after the interval could be connected to the extrapolated first part of the curve.

One of the diodes was connected to a pen recorder and the effect of the interruption of the irradiation when the connection of the various diodes

Table

The initial sensitivity of the diodes measured with 1 MΩ in load resistance — The D₅₀ dose is the dose which causes 50 % loss in sensitivity

Diode type	Number	Initial sensitivity (μV/R/min) ⁶⁰ Co	D ₅₀ M rad
Siemens BPY 11	1	53.1	0.37
	2	59.0	0.32
	3	55.9	0.15
	4	41.1	0.26
	5	59.0	0.19
Siemens BPY 100	1	12.4	0.23
	2	16.2	0.24
	3	17.9	0.12
	4	19.3	0.16
	5	23.1	0.24
Hoffmann B 120 CG 9	1	36.0	0.52
Hoffmann N 120 CG 9	1	23.7	0.58

Depth dose measurements have been performed in a water phantom and compared with results obtained with a small ionization chamber (BENNETT et al. 1959). This chamber is 3 mm in diameter, and its calibration factor decreases with increasing energy, a factor of 1.16 between ⁶⁰Co and roentgen radiation with HVL 0.1 mm Cu. As may be seen from Fig. 4, the agreement between the chamber and the diode for ⁶⁰Co irradiation is complete, and for the roentgen beam the maximum deviation between the chamber and diode is less than 3 % up to 20 cm depth. The reason why the difference is so small in spite of the great energy dependence of the probe measured free in air (HERTZ & GREMMELMAIER 1960) is that the spectral distribution of primary and secondary radiation does not to any great extent change with depth.

The penumbra of the ⁶⁰Co beam has been measured with the chamber and the diode. A lead block 2 cm × 11 cm × 8 cm was inserted at the centre of the field, just outside the collimator of the apparatus, and the cross section of the beam was measured in the phantom. The diode gave 8 % higher dose just below the lead block, as compared to the chamber. These measurements indicate that the diode can be used for depth dose measurements in homogeneous phantoms but when a considerable change in the spectral distribution of the radiation is suspected, the measurements may be influenced by the energy dependence of the silicone diode.

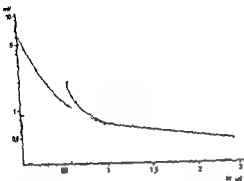


Fig 5 Radiation damage effect at Couradation measured for a BPY 100 diode No 4

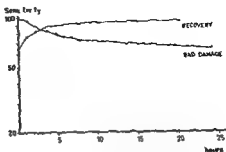


Fig 6 Loss of sensitivity as a function of the irradiation time for a Hoffmann sil con solar cell N 120 CG 9 and the recovery as a function of the time after finishing the irradiation

Sensitivity and radiation damage The initial sensitivity of the various diodes are shown in a Table. The diodes were irradiated with a ^{60}Co beam, with an exposure rate of 320 R/min. It is well known that when the energy of the secondary electrons is sufficient (>250 keV) they can produce interstitial vacancy pairs (Frenkel defects) and other changes in the silicon and thus change the sensitivity of the diode. These defects can produce donor and acceptor energy levels within the energy gap. The effect is however more complex than that (DEARVALE 1964). Several investigations on these effects in p-n junctions have been reported (WILLPTON & WATSON 1963; ROSENZWEIG 1962).

To investigate the radiation damage effect for ^{60}Co radiation 5 BPY 11 diodes and 5 BPY 100 diodes were mounted on a perspex plate and irradiated simultaneously at 320 R/min. In the Table the D_{50} doses obtained are indicated i.e. the doses which reduce the sensitivity to 50% of the initial sensitivity. The irradiations were performed in two sessions and the signals were measured with a load resistance of 1 M Ω . The diodes were irradiated in the first session for 28 hours and after an interval of 96 hours they were irradiated again for 47.5 hours.

An example of the curve for one of the diodes is given in Fig 5. As will be seen from the figure the sensitivity of the diode increased during the period without irradiation. In all the ten figures obtained it was obvious that the curve after the interval could be connected to the extrapolated first part of the curve.

One of the diodes was connected to a pen recorder, and the effect of the interruption of the irradiation when the connection of the various diodes

Table

The initial sensitivity of the diodes measured with 1 MΩ in load resistance — The D_{50} dose is the dose which causes 50 % loss in sensitivity

Diode type	Number	Initial sensitivity ($\mu\text{V/R/min}$) * Co	D_{50} M rad
Siemens BPX 11	1	53.1	0.37
	2	59.0	0.37
	3	55.9	0.15
	4	44.1	0.26
	5	59.6	0.19
Siemens BPX 100	1	12.4	0.23
	2	16.2	0.24
	3	17.9	0.12
	4	19.3	0.16
	5	23.1	0.24
Hoffmann III 120 CG 9	1	36.0	0.52
Hoffmann N 120 CG 9	1	23.7	0.58

Depth dose measurements have been performed in a water phantom and compared with results obtained with a small ionization chamber (BENNETT et coll. 1959). This chamber is 3 mm in diameter, and its calibration factor decreases with increasing energy, a factor of 1.16 between ^{60}Co and roentgen radiation with HVL 0.1 mm Cu. As may be seen from Fig. 4, the agreement between the chamber and the diode for ^{60}Co irradiation is complete, and for the roentgen beam the maximum deviation between the chamber and diode is less than 3 % up to 20 cm depth. The reason why the difference is so small in spite of the great energy dependence of the probe measured free in air (HERTZ & GREMMELMAIER 1960) is that the spectral distribution of primary and secondary radiation does not to any great extent change with depth.

The penumbra of the ^{60}Co beam has been measured with the chamber and the diode. A lead block 2 cm \times 8 cm \times 8 cm was inserted at the centre of the field, just outside the collimator of the apparatus, and the cross section of the beam was measured in the phantom. The diode gave 11 % higher dose just below the lead block, as compared to the chamber. These measurements indicate that the diode can be used for depth dose measurements in homogeneous phantoms but when a considerable change in the spectral distribution of the radiation is suspected, the measurements may be influenced by the energy dependence of the silicone diode.

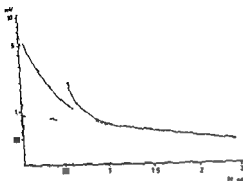


Fig 5 Radiation damage effect at Courradiation mea ured for a BPY 100 diode No 4

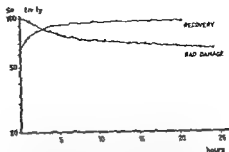


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One of the diodes was connected to a pen recorder and the effect of the interruption of the irradiation when the connection of the various diodes

to the voltmeter was made, could be studied. A 45 min interval in the irradiation, for instance, with the same exposure rate, gave an increase in voltage from 3.25 to 3.30 mV. This increase had however disappeared after 6 min of irradiation, and the curve coincided with the extrapolation of the initial curve. The curves for the diodes seem to be divided in two exponential components, a rapid one and a slower one, as indicated in the figure. The doses seem to be too small, however, to enable a more accurate analysis of these phenomena.

The two Hoffman solar cells were also irradiated, and they showed more resistance to radiation damage than the BPY 11 and BPY 100 diodes, as may be seen from the Table. The diode named radiation resistant showed a slight increase in sensitivity (3 %) after 60 000 rad. The D_{50} for the Hoffmann diodes was found to be the same as for the International Rectifier diode ($D_{50}=500\,000$ rad) measured by WHELPTON & WATSON (1963).

To study the effect of fractionation of the dose, a N 120 CG 9 diode was irradiated with a total dose of 228 000 rad at 200 R/min, fractionated with intervals of 10 min irradiation and 20 min pause. This dose decreased the sensitivity by 14 %. For the N 120 CG 9 diode in the Table, the corresponding decrease in sensitivity for the same exposure was 20 %.

The effect of recovery was investigated with a N 120 CG 9 diode, and the result is plotted in Fig. 6. The diode was connected to the voltmeter and a pen recorder, and was irradiated to a loss in sensitivity of 36 % at an exposure rate of 720 R/min. After the irradiation, the cobalt apparatus and the recorder were automatically triggered for 15 seconds at certain intervals in order to get a signal from the diode. As will be seen from the figure, the diode sensitivity recovered from 64 % to 94 % after 20 hours. Some defects produced in the silicon crystal are stable at room temperature but the diode can recover on annealing (MOODY *et al.* 1958, BEMSKI & AUGUSTYNIAK 1957). It may be observed that the recovery at room temperature does not seem to be 100 %.

Conclusions

It may be concluded that the use of the commercial diodes studied in this investigation should be restricted unless the parameters investigated can be kept under control. The temperature effect can be controlled either by measuring the temperature, for instance with a thermistor, or by measuring the short circuit current, making the diode independent of temperature and exposure rate but less sensitive. The energy dependence is not observable, for instance when determining depth dose curves in a homogenous phantom with ^{60}Co ,

but care must be taken when the spectral distribution varies so much that the energy dependence may influence the measurement

The most serious effect is the radiation damage which influences the reproducibility of the diodes. The measurements performed have shown this phenomenon to be a complex one. Radiation damage occurs also with the LiF dosimeter (MARRONE & ATTIX 1964). The sensitivity is good enough to make the diodes suitable for measurement of doses from an ordinary ⁶⁰Co apparatus used in the clinic. Exposure rates may be measured at least down to 1 R/min. The lithium drifted diodes investigated by BAILY & KRAMER (1964) seem to be more sensitive however than the photodiodes used in the present investigation.

SUMMARY

Some commercial photodiodes have been tested for use in clinical dosimetry. The following parameters were investigated: sensitivity, exposure rate dependence, temperature dependence, energy dependence and radiation damage. The most serious disadvantage was the radiation damage effect which influences the sensitivity.

ZUSAMMENFASSUNG

Kommerzielle Photodioden wurden mit Hinsicht auf die Verwendung in der klinischen Dosimetrie geprüft. Die folgenden Parameter wurden studiert: Sensitivität, Abhängigkeit von der Dosisleistung, Temperatur und Energie Abhängigkeit und Bestrahlungsschaden. Der letztgenannte Effekt war der grösste Nachteil, da die Sensitivität dabei beeinflusst wird.

RÉSUMÉ

Les auteurs ont expérimenté pour la dosimétrie clinique des photodiodes du commerce. Les paramètres étudiés sont: la sensibilité, la dépendance à l'égard du débit de dose, de la température, de l'énergie et leur détérioration par les radiations. Le plus sérieux inconvénient est leur détérioration par les radiations, que influe sur leur sensibilité.

REFERENCES

- BAILY N. and KRAMER G. The lithium-drifted silicon p-n junction as an X-ray and gamma ray dosimeter. *Radiat. Res.* 27 (1964) 53.
 BRISKI G. and ALGUSTYNIAK H. W. Annealing of electron bombardment damage in silicon crystals. *Phys. Rev.* 108 (1957) 645.
 BENNER S., RAVENHILL J. and GEBERT G. Miniature ionization chambers for measurements in body cavities. *Phys. in Med. Biol.* 4 (1959) 26.

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RADIATION PROTECTION MEASUREMENTS FOR A 17 MeV BETATRON

by

P E ÅSARD

This paper presents the results of measurements of the radiation milieu around a Siemens 17 MeV betatron (GUND & BERGER 1953) for clinical use. Radiation protection measurements for this type of betatron have previously been reported by POHLIT (1961), BREITLING & SEEGER (1962) and VETTORI & PICORINI (1963). The unwanted radiation produced outside the primary beam consists of three components: roentgen rays, electrons (negatrons and positrons) and neutrons. Roentgen rays are generated when electrons are decelerated in filters, target, collimator, doughnut and magnet. The electrons come from photoelectric, Compton and pair production processes in the parts of the betatron mentioned above and from electrons having sufficient energy to leave the doughnut and the shielding of the betatron.

Fast neutrons are produced by photonuclear and electrodisintegrating processes especially in the lead collimator and the beam flattening filter. For neutron production in high Z materials a threshold energy exists for the roentgen rays or the electrons, and this is as a rule larger than 6–8 MeV. The neutron yield is less by a factor of approximately 1/137 (BROWN & WILSON 1954) for electrons compared to roentgen rays. The greatest neutron intensity

- CALKINGS J : Photovoltaic cells measure radiation for medical therapy *Nucleonics* 20 (1962) 70
- DEARNALEY G : Radiation damage effects in semiconductor detectors *Nucleonics* 22 (1964), 78
- GULDBRANDSEN T and MADSEN C II : Radiation dosimetry by means of semiconductors *Acta radiol* 58 (1962), 226
- HERTZ C H and GREMMELMAIER R : Miniature semiconductor dose ratemeter *Acta radiol* 54 (1960), 69
- JONES A R : The application of some direct current properties of silicon junction detectors to γ ray dosimetry *Phys in Med Biol* 8 (1963), 451
- MARRONE M J and ATTIX F H : Damage effects in CaF_2 , Mn and LiF thermoluminescent dosimeters *Health Phys* 10 (1964), 431
- MOODY J W, KENDALL C L and WILLARDSSEN R K : Photovoltaic gamma ray dosimeter *Nucleonics* 16 (1958), 101
- ROSENZWEIG W : Silicon solar cells as versatile radiation dosimeters *Rev Sci Instr* 33 (1962) 379
- SCHARF K and SPARROW J H : Steady state response of silicon radiation detectors of the diffused p n junction type to λ rays I : Photovoltaic mode of operation *NBS J Res Physics and Chemistry* 68 A 6 (1964) 683
- WHEELPTON D and WATSON B W : A p n junction photovoltaic detector for use in radiotherapy *Phys in Med Biol* 11 (1963) 33

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Table 1

Measurements in broad beam geometry of the electronic equilibrium conditions in a double chamber irradiated with ^{60}Co — Exposure rate 7.6 mR/min

Perspex cover mm	Exposure mR	Response in %
0	104	100
1.5		97.7
3.2		97.0
4.5		97.4
6.0		97.4
8.2		95.7

Table 2

Measurements of the electronic equilibrium conditions in a double chamber irradiated with stray radiation from the betatron — Primary beam 16 MeV electrons

Perspex cover mm	Response 0 mm perspex
	Response 4 mm perspex
1	1.00
2	1.08
4	1.08

is found in the primary roentgen ray beam, where they are produced in the beam flattening filter and the lead collimator (LAUGHLIN 1951, HOFMANN 1955). The threshold energy for neutron production is for $^{208}\text{Pb}(\gamma, n)$ 8.2 MeV, for $^{207}\text{Pb}(\gamma, n)$ 6.8 MeV and about 7.4 MeV for $^{209}\text{Pb}(\gamma, n)$ with the resonance energy at about 14 MeV (GORYACHEV 1964).

Measuring techniques The so called double chambers (WALSTAM 1965) have been used for the measurement of roentgen rays and electrons. The range is 10 to 200 mR for the outer chamber and 200 to 2 000 mR for the inner chamber when using the ordinary charging potential of 90 volt. The chambers in PVC plastic containers, with 0.7 mm thick walls, have been calibrated free in air with a ^{60}Co source mounted in a lead collimator. The exposure rate at a distance of 1 m from the source was 7.6 mR/min. To estimate the wall thickness required to give electronic equilibrium conditions a chamber was placed in perspex containers with walls of different thicknesses. As will be seen

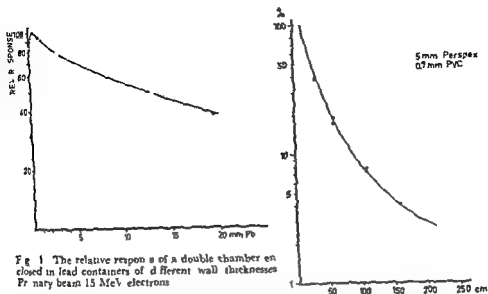


Fig 2 (right diagram) Relative dose rates of stray radiation at different distances from the betatron head with double chambers enclosed in different containers. The measurements were made along a line in the horizontal plane through the betatron head and the plane of the doughnut (in the direction towards the right wall as seen in fig 6).

from Table 1 no increase in response due to electronic build up could be demonstrated. This is in good agreement with the results reported by WALSTAM (1965) for chambers exposed in broad beam geometry. For the measurements in the betatron 20 chambers showing the same calibration factor within $\pm 5\%$ were chosen.

Measurements free in air of the electronic equilibrium condition were also performed outside the primary beam of the betatron at 16.0 MeV electron irradiation with a chamber placed 1.5 m from the head of the betatron. As will be seen from Table 2 no increase in response with increasing wall thickness indicating electronic build up could be demonstrated. This is due to the heterogeneity of the radiation and the irradiation geometry. When the chamber was placed in different containers of lead however a small increase in the response of the chamber with increasing wall thickness was found (Fig 1). In these measurements the primary beam was 15 MeV electrons and the chamber was placed 5 cm from the head of the betatron.

As the chambers were intended to be used for dose distribution measurements of the stray radiation in the treatment room measurements were performed with chambers at different points in the treatment room with the thin PVC

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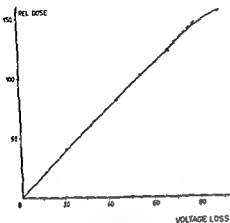


Fig 3 Response of the inner chamber for stray radiation at a dose rate of 5.800 mrad/min

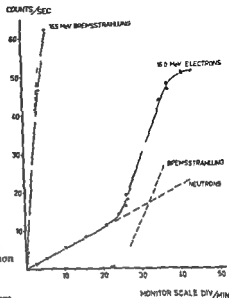


Fig 4 (right diagram) Measurements with the rem counter just outside the door to the treatment room. Primary beam 16.5 MeV roentgen rays and 16 MeV electrons. Monitor scale divisions/min is the relative dose rate in the primary beam.

corresponding to discharges from 10 to 90 volt, and it can be seen from Fig 2 that the recombination loss became apparent when the rest potential was less than 30 to 20 volt.

The radiation around a betatron is complex, and the R unit cannot be used in the measurements partly because of the electron contamination and partly because of the high energy of the roentgen rays. The dose rate in rad/min in water could have been used if the spectra of the electrons and the electromagnetic radiation were known. This is not the case and the appropriate stopping powers are thus unknown. For that reason the unit used in the measurements with the chambers was rad/min in air. Phantom measurements have been performed in cases where a more accurate estimate of doses outside the primary beam was needed for a patient. In calculating rad/min in air, the approximation has been made that the constants $R/volt$ from the ^{60}Co calibrations were used in the measurements for the betatron. This may be expressed

$$D_{17} = 0.87 \Delta V (Q/volt) \sim 0.87 \Delta V (R/volt)_{^{60}Co} \text{ rad}$$

where ΔV = voltage discharge and $Q = \text{esu}/0.001293 \text{ g air}$

The outer chambers have never been discharged to less than 40 volt in order to eliminate recombination losses.

Table 3

Response of the outer chamber with stray radiation from the betatron at a dose rate of 85 mrad/min

Charging voltage voltage	Chamber 581	Chamber 582
	Response 90 V	Response 90 V
	Response V	Response V
90	1.00	1.00
60	1.07	1.01
40	1.22	1.17

plastic containers and with perspex containers of 0.5 cm wall thickness. An example of the results is shown in Fig. 2. The chambers were placed at different distances from the betatron head and exposed to the stray radiation with 16 MeV electrons as primary beam. As will be seen from Fig. 2, the relative response between chambers in perspex containers and in PVC containers is practically the same regardless of the distance from the betatron. In the measuring points at 160 and 210 cm from the betatron the response in chambers placed in PVC containers were 8 to 9 % higher, as compared to chambers in the perspex containers. This is probably due to scatter from the walls, absorbed in the perspex containers but not in the PVC containers. The differences obtained were so small that they may be neglected for the measurements of the dose distributions in the treatment room, and therefore in all the measurements reported below chambers with PVC containers have been used.

Measurements of the recombination losses have been performed in both the outer and the inner chamber, the results are shown in Table 3 and Fig. 3, respectively. In the measurements of the recombination in the outer chamber, four chambers were placed 1.5 m from the betatron head. The dose rate was 85 mrad/min in air with 16 MeV electrons as primary beam. Two double chambers were charged at each measurement with 90 volt, and the charge voltage in the other two chambers was varied as is shown in Table 3. The dose was constant and corresponded to a decrease in voltage from 90 to 60 volt. The measured recombination was larger than could be expected from theoretical estimations (WALSTAM 1965). These estimates did not, however, take into account the inhomogeneities of the electric field in the chambers.

The recombination in the inner chamber was investigated by exposing a chamber charged to 90 volt in contact with the betatron head where the dose rate was 5.800 mrad/min. The chamber was irradiated with different doses

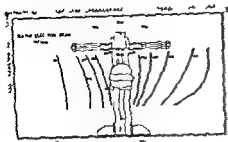


Fig 7 Dose rate distribution in a vertical plane through the betatron head. Dose rate in the primary beam (16 MV electrons) 200 rad/min

Bremsstrahlung intensity reaches such a level with this intensity in the electron beam that it gives detectable counts in the BF₃ counter. The intensity from the roentgen rays in the proportional counter at 20 scale divisions/min on the betatron monitor was equal to about 110 mR/hr. This corresponds to a mean exposure rate during the betatron pulse of 140 R/hr. The reason why the roentgen ray component did not influence the counter at maximal output (about 7 scale divisions/min) with the 16.5 MV roentgen beam is that the exposure rate in the rem counter was some 7 times less in that case than in the case of the maximal output with the 16.0 MeV electron beam (corresponding to about 44 scale divisions/min).

The curve for 16.0 MeV electrons seems to become constant at higher exposure rates independent of the intensity of the primary beam. This depends on the fact that the counts produced by the roentgen rays block the counter for the neutrons. The counting rate is not however exactly 50 counts/sec but a little higher. The explanation is that neutrons reaching the proportional counter more than 20 μ sec after the leading edge of the betatron pulse then give counts because the counter is not blocked. At higher neutron dose rates the plateau would occur at a greater height. This was investigated by irradiating the rem counter with the same primary electron beam first with the counter in contact with the betatron head and then with the counter placed inside the treatment room at the right wall. In the first case 89 counts/sec were observed at dose rates larger than 20 scale divisions/min and in the second case 57 counts/sec. The rem counter was not used for dose distribution measurements in the treatment room because of the errors caused by the high intensities of the roentgen rays.

Results

Measurements in the treatment room. The dose distribution in the treatment room was measured for the 16.5 MV roentgen beam, filter 2, collimator B2, field size 5.9 cm diameter at FSD = 50 cm and with the 16.0 MeV electron

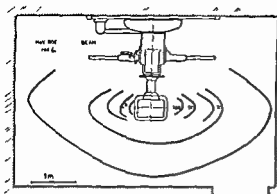


Fig 5 Dose rate distributions of the stray radiation in a horizontal plane through the betatron head. Dose rate in primary beam (16.5 MV roentgen rays) 27 rad/min at FSD = 50 cm

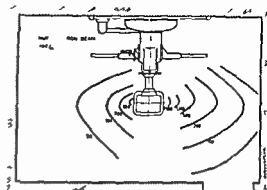


Fig 6 Dose rate distribution in a horizontal plane through the betatron head. Dose rate in the primary beam (16 MeV electrons) 200 rad/min

For the measurements of neutrons, a rem counter (ANDERSON & BRAUN 1964) from AB Atomenergi (Studsvik, Sweden) has been used. This rem counter has a dose response between neutron energies of 0.025 eV to 10 MeV which follows the ICRP (1955) rem response curve. The detector consists of a BF₃ proportional counter embedded in a moderator of polyethylene and boron plastic. A dose rate of 1 mrem/hr gives 2.4 pulses/sec with a pulse length of 20 μ sec. The dose rate can also be read on a logarithmic ratemeter from 0.1 to 100 mrem/hr.

To test the linearity of the instrument with pulsed radiation it was placed just outside the door to the treatment room (Fig 8), and the number of pulses per sec were measured as a function of the relative dose rate in the primary beam at 16.5 MV roentgen radiation and 16.0 MeV electrons. The results of the measurements are shown in Fig 4.

The response of the rem counter when the primary beam was 16.5 MV roentgen radiation, showed a nonlinearity at counting rates larger than 30 counts/sec, that is, equivalent to 12.5 mrem/hr. The mean dose rate during the pulse ($\sim 5 \mu$ sec in length, 50 pulses/sec) was however much larger, namely $5 \cdot 10^4$ mrem/hr. This finding is in agreement with the data sheet of the rem counter, for which 10^4 pulses/sec are given as an upper limit for the instrument.

In the measurements with 16.0 MeV electrons as the primary beam there was a break in the curve at 20 scale divisions/min on the betatron monitor, as seen in the figure (For these measurements, the chamber was in the same position outside the door). The explanation of this phenomenon is that the

Table 4

Dose rate just outside door to treatment room as a function of the energy of the primary electron beam—Same filter and field size at all energies

MeV	mrads/mm	mrads/krad
6	1.2	7.5
9	1.7	7.7
12	3.7	10.2
16	5.0	13.5

* mrads/krad means the dose at the measuring point per krad in primary beam

at point B, Fig. 5, with 16.5 MV roentgen beam and a treatment distance of 50 cm is shown in Table 6. It is evident from these measurements that filter and field size had a negligible effect on the dose rate at point B. There was no primary beam.

Measurements of doses to patients. In some cases it can be useful to know the dose to the patient outside the primary beam, especially to certain organs. This is particularly important when the patient is of fertile age.

A technique for electron irradiation of retinoblastoma in children has been developed at Radiumhemmet (HULTZBERG *et al.* 1965). The dose to the eye not intended to be irradiated has been measured with a chamber covered with 2 mm perspex placed in a phantom. The result was that the lens received 6 to 7 rad per krad given to the other eye. Doses to the gonad and testicle have also been measured, giving 60 to 80 mrad per krad. A slight increase in the doses of about 10% was found when the phantom was placed parallel with the plane of the doughnut.

Measurements in the control room. The dose rates from neutrons were measured at points 1.5 m above the floor. Just outside the door, which is insufficiently protective, the neutron dose rate with the 16.5 MV roentgen beam was 20 mrem/hr (corrected for dead time losses in the rem counter) and with the 16.0 MeV electron beam it was 10 mrem/hr. The dose rates at other points in the control room are given in Fig. 8. The deflections of the neutrons in air and walls caused a higher dose rate at the opposite wall of the room than found in the vicinity of the wall of the treatment room. The protection in this area will be improved.

beam filter 6 (0.2 mm Pb), tube of 8 cm diameter. The dose rate in the primary beam was 27 mrad/min at FSD = 50 cm and 200 mrad/min, respectively. The chambers were placed on a wooden support and 20 were exposed simultaneously. A mix-D body phantom was placed on the treatment couch in all the measurements. The results are given in Figs 5 to 7.

In the place of the doughnut the intensity is at a maximum. The distribution is not symmetrical around the betatron head in the case of 16 MeV electrons as primary beam. The intensity has a maximum on that side in the plane of the doughnut where the primary beam is taken out, and is 4 to 6 times higher than the dose rate on the other side. The reason for the high intensity is that only about 4 % of the electrons present in the doughnut during the acceleration are present in the primary beam. The rest of the electrons are lost producing ionization and roentgen radiation. About 50 % of the electrons which hit the anticathode are lost (GUND & SCHITTENHELM 1953).

A high intensity was also found in the direction opposite to the primary beam. The magnet does not absorb the radiation produced in that direction. VETTORI & FIGORINI (1963), for the same type of apparatus, reported a maximum in the vicinity of the injector. These authors also divided the stray radiation into soft (mainly electrons) and hard components. The soft component of the stray radiation of a 15 MeV primary electron beam is totally absorbed after ~ 4 g/cm². The half value layer of the hard component was found by measurement to be 13 mm Pb. This value is in good agreement with the measurements recorded in Fig. 1, showing that 12 mm Pb causes a 50 % reduction of the maximum intensity. These measurements are not directly comparable, however, because of the different geometries.

The dose rate just outside the door to the treatment room, as a function of the energy of the primary electron beam when using filter 5 (0.1 mm Pb) and a tube of 5 cm diameter, is shown in Table 4. In this table, mrad/krad means the dose at the measuring point when a maximum dose of 1 krad is given to the patient.

The ratio mrad/krad is strongly dependent on which filter is used, as may be seen from Table 5. These measurements were performed at point A, Fig. 7, with the 16 MeV electron beam. The dose rate at point A is practically independent of filter and field size, but the dose per krad varies with a factor 6 to 7 between filter 0 and filter 8. A thicker filter results namely in a larger decrease in dose rate for the primary beam, and thus a longer time is needed for any given dose to the patient, while the intensity of the stray radiation depends on the fact that only a small and fairly constant fraction of the accelerated electrons actually reach the primary beam, independent of the filter used.

The dependence of beam flattening filters and field sizes on the dose rate

Table 4

Dose rate just outside door to treatment room as a function of the energy of the primary electron beam — Same filter and field size at all energies

MeV	mrad/min	mrad/krad
6	1.7	7.5
9	1.7	7.7
12	3.7	10.2
16	5.0	13.5

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The dependence of beam flattening filters and field sizes on the dose rate

Table 4

Dose rate just outside door to treatment room as a function of the energy of the primary electron beam — Same filter and field size at all energies

MeV	mrad/min	mrad/krad ¹
6	12	7.5
9	17	7.7
12	37	10.2
16	50	13.5

¹ mrad/krad means the dose at the measuring point per krad in primary beam

at point B Fig. 5 with 16.5 MV roentgen beam and a treatment distance of 50 cm is shown in Table 6. It is evident from these measurements that filter and field size had a negligible effect on the dose rate at point B. There was no primary beam.

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Table 5

The dependence of filters and field sizes on the dose rate at point A (Fig. 7) — Primary beam 16 MeV electrons

Filter	Tube cm diam	mrad/min	mrad/krad [†]
0	8	111	130
4 (3 10^{-3} /mm Au)	8	108	190
II (0.6 mm Pb)	8	120	850
III	3	112	580

* mrad/krad means the dose in point A per krad in primary beam

Table 6

The dependence of beam flattening filters on the dose rate at point B (Fig. 5) — Primary beam 16.5 MV roentgen rays

Filter	Collimator	mrad/min	mrad/krad
0	B 2	57	—
2	B 2	62	1300
3	B 2	60	1500
0	Collimator closed	58	—

* mrad/krad means the dose in point B per krad in the primary beam

Discussion

It may be noted on the basis of these measurements that even if the dose rate from the stray radiation may be as much as 10 times larger with 16.0 MeV electrons, compared to the dose rate with 16.5 MV roentgen irradiation, the dose outside the beam per rad in the primary beam may be about the same. With small field sizes, when a thin filter can be used for the electron beam, the dose from stray radiation per rad in the primary beam is generally less compared with the roentgen beam.

In the measurements around the betatron, differences in dose rates in different directions from the betatron head were estimated, these can have some economic consequences in the calculation of thicknesses of walls and roof and with respect to the position of the betatron in the treatment room. POHLIT (1961) has pointed out that the distribution of roentgen radiation around the betatron is not influenced to any great extent by the size of the room, and measurements can therefore be generalized. This does not apply to neutrons,



Fig. 8 Dose rate from fast neutrons in the control room adjacent to the treatment room. Dose rate in primary beam (16.5 MV Bremsstrahlung) 27 rad/min at FSD = 50 cm

however. The doses to patients outside the primary beam seem to be negligible in the cases investigated. This applies also to the higher energies available on our betatron (VETTORI & FIGORINI 1963). AZUMA (1963) has measured the contamination of electrons in a 17 MeV roentgen beam from a Siemens betatron and pointed out that the eyes can be protected from the electrons by an absorber 5 g/cm² thick.

The qualities of the rem counter can be improved for use with pulsating irradiation for instance by decreasing the dead time and thus enabling higher dose rates to be measured. The level of the discriminator can also be changed thereby making it possible to some extent to discriminate pulses produced by the roentgen radiation (LYDEN 1965).

SUMMARY

The dose distribution from stray radiation around a Siemens 17 MeV betatron was measured and the dependence on radiation type, energy, filter and field size, and doses to critical organs using a special irradiation technique, have been studied. Doses from neutrons in an adjacent room and the suitability of the instrument used in pulsating beams were studied with a rem counter.

ZUSAMMENFASSUNG

Die Dosisverteilung der Streustrahlung um einen Siemens 17 MeV Betatron wurde bestimmt. Die Abhängigkeit von Bestrahlungsart, Energie, Filter und Feldgrösse mit Hinsicht auf die Dosis für strahlensensible Organe wurde mittels einer speziellen Bestrahlungstechnik untersucht. Die Neutronendosis von einem naheliegenden Zimmer wurde mit einem rem-Zähler gemessen und die Verwendbarkeit dieses Instrumentes wenn in einem pulsierenden Strahlenbündel verwendet wurde studiert.

RÉSUMÉ

La distribution de dose du rayonnement diffusé autour d'un béatron Siemens de 17 MeV a été mesurée. L'auteur a mesuré la dépendance de cette distribution de dose à l'égard du type d'irradiation, de l'énergie du filtre et des dimensions du champ ainsi que les doses aux organes critiques avec une technique spéciale d'irradiation. Il a étudié avec un compteur rem les doses dues aux neutrons dans la pièce adjacente et la fiabilité de cet instrument dans les rayonnements pulsés.

REFERENCES

- ANDERSON I Ö and BRAUN J. A neutron rem counter with uniform sensitivity from 0.025 eV to 10 MeV. *Atomenergi Report AE 132* (1961)
- AZUMA J. Über das Auftreten einer sekundären Elektronenstrahlung bei der Bestrahlung mit der ultraharten Röntgenstrahlung des Betatrons. *Strahlentherapie* 122 (1963), 37
- BREITLING G und SPOER W. Störstrahlung am 18 MeV SRW Betatron. *Strahlentherapie* 118 (1962), 630
- BROWN K. L. and WILSON R. Electrodintegration of Cu^{63} , Zn^{64} , Ag^{109} and Ta^{181} . *Phys Rev* 93 (1954), 113
- GORYACHEV B. J. Cross sections of photonuclear reactions. Tabulated experimental data. *Atomic Energy Review* 2 (1964) 71 No 2
- GUND K. und BERGER H. Die 15 MeV Elektronenschleuder für medizinische Anwendung der Siemens Reiniger Werke. *Strahlentherapie* 92 (1953), 489
- und SCHITTNEHRM R. Die physikalischen Eigenschaften der Strahlenbündel der 15 MeV Elektronen Schleuder der Siemens Reiniger Werke. *Strahlentherapie* 92 (1953) 505
- HOFFMANN D. Strahlenschutzmessungen über die beim Betrieb einer 15 MeV Elektronen Schleuder durch Neutronen verursachte Zusatzdosis. *Strahlentherapie* 97 (1955) 239
- HULTBERG S, WALSTAM R. and ÅSARD P. E. Two special applications of high energy electron beams. *Acta radiol Ther Phys Biol* 3 (1965) 287
- LAUCHLIN J. S. Considerations in the use of a 23 MeV medical betatron. *Nucleonics* 4 (1961) 5 No 8
- LYDÉN A. Personal communication (1965)
- POHLEIT W. Standardisierung der Dosismessung bei energiereichen Strahlungen. Georg Thieme Verlag Stuttgart 1961
- Dosimetrie zur Betatrontherapie. Georg Thieme Verlag, Stuttgart 1965
- WALSTAM R. Studies on therapeutic short distance and intracavity gamma beam techniques. *Acta radiol* (1965) Suppl. No 236
- VITTORI P. G. P. und PIRORINI I. Untersuchungen über die Störstrahlung um ein Betatron während der Bestrahlung mit schnellen Elektronen. *Strahlentherapie* 121 (1963) 6

PRODUCTION OF ^{18}F FOR BONE SCANNING

by

LAURI PATOMÄKI

The first application of ^{18}F to biologic work was made in 1940 but the use of the isotope was rendered difficult by the fact that only small activities could be produced (BERNSTEIN & KATZ 1953). It was later observed (KNIGHT NOVEL CANOV & TURKEVICH 1951) that ^{18}F could be produced in a thermal reactor by the irradiation of a compound containing both lithium and oxygen. Since then the production of quite large activities on an economic basis has been easy.

If no commercial radiochemical processing laboratories are near ^{18}F may be prepared on the spot provided a thermal reactor with a flux of the order of 10^{14} n/s cm² such as is frequently available in universities and training institutes lies within 20 km of the clinic. The half life of only 110 min of ^{18}F may then possess few disadvantages. The practical preparation of ^{18}F in the normal isotope laboratory of a radiotherapy clinic was the aim of this work. The isotope should be in a form suitable for in vivo studies particularly when it is required for oral administration in bone scanning.

The production of ^{18}F A number of nuclear reactions result in the production of ^{18}F activity such as $^{18}\text{O}(p,n)^{18}\text{F}$ in cyclotrons and reactors (CARLSON et coll 1959, NUSYNOWITZ et coll 1965). In thermal reactors production can be of

RÉSUMÉ

La distribution de dose du rayonnement diffusé autour d'un bétatron Siemens de 17 MeV a été mesurée. L'auteur a mesuré la dépendance de cette distribution de dose à l'égard du type d'irradiation, de l'énergie, du filtre et des dimensions du champ ainsi que les doses aux organes critiques avec une technique spéciale d'irradiation. Il a étudié avec un compteur rem les doses dues aux neutrons dans la pièce adjacente et la fiabilité de cet instrument dans les rayonnements pulsés.

REFERENCES

- ANDERSON I Ö and BRAUN J : A neutron rem counter with uniform sensitivity from 0.025 eV to 10 MeV. *Atomenerg. Report AE 132* (1964)
- AZUMA J : Über das Auftreten einer sekundären Elektronenstrahlung bei der Bestrahlung mit der ultraharten Röntgenstrahlung des Betatrons. *Strahlentherapie* 122 (1963) 37
- BREITLING G und SEEGER W : Störstrahlung am 18 MeV SRW Betatron. *Strahlentherapie* 118 (1962) 630
- BROWN K L and WILSON R : Electrodissintegration of Cu^{63} , Zn^{64} , Ag^{109} and Ta^{181} . *Phys. Rev.* 93 (1954) 443
- GORYACHEV B J : Cross sections of photonuclear reactions. Tabulated experimental data. *Atomic Energy Review* 2 (1964) 71 No 2
- GUND K und BERGER H : Die 15 MeV Elektronenschleuder für medizinische Anwendung der Siemens Reiniger Werke. *Strahlentherapie* 92 (1953) 489
- und SCHITTENHELM R : Die physikalischen Eigenschaften der Strahlenbündel der 15 MeV Elektronen Schleuder der Siemens Reiniger Werke. *Strahlentherapie* 92 (1953) 505
- HOFFMANN D : Strahlenschutzmessungen über die beim Betrieb einer 15 MeV Elektronen Schleuder durch Neutronen verursachte Zusatzdosis. *Strahlentherapie* 97 (1955) 239
- HULTBERG S, WALSTAM R and ASARD P E : Two special applications of high energy electron beams. *Acta radiol. Ther. Phys. Biol.* 3 (1965) 287
- LAUGHLIN J S : Considerations in the use of a 23 MeV medical betatron. *Nucleonics* 4 (1951) 5 No 8
- LYDEN A : Personal communication (1965)
- POHLIT W : *Standardisierung der Dosismessung bei energiereichen Strahlungen*. Georg Thieme Verlag Stuttgart 1961
- *Dosimetrie zur Betatrontherapie*. Georg Thieme Verlag Stuttgart 1965
- WALSTAM R : Studies on therapeutic short distance and intracavity gamma beam techniques. *Acta radiol.* (1965) Suppl. No 236
- VETTORI P G P und PICORINI F : Untersuchungen über die Störstrahlung um ein Betatron während der Bestrahlung mit schnellen Elektronen. *Strahlentherapie* 121 (1963) 6

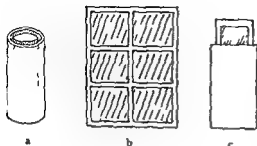


Fig 2 Forms of sample packages used in the neutron irradiation a) Cylindrical sample made of plastic b) Flat sample made of plastic c) Sample of aluminium Shaded areas refer to Li_2CO_3

then precipitated. The phosphate is filtered off in a glass filter (5 to 15 microns) and washed. Tritium and lithium are thus separated from ^{18}F . The phosphate is dissolved in 5 ml 2.7 normal (warmed) HCl in the filter. Finally about 10 ml of concentrated $\text{Na}_2\text{C}_2\text{O}_4$ is added for adjustment of the pH to about 4. The solution is now ready for oral use.

This method differs slightly from the one described by ANBAR (1963).

The final solution usually carries an activity of 1 mCi of ^{18}F per 3 g of irradiated lithium carbonate. From the moment the sample is taken out of the reactor 6 km from the clinic one hour has elapsed. Chemical separation by the method described takes about 20 minutes. The yield is usually about 80%. If the solution is to be used for intravenous injection it must be neutralized, and no citrate should be added (ANBAR 1963; DWORNIK et al 1955; THOMAS et al 1965).

Form and size of the sample during neutron irradiation. The size of the lithium carbonate sample greatly influences the specific activity achieved at neutron irradiation by reason of the large cross section of ^6Li to thermal neutrons. If the thickness of the sample should exceed 2 mm the specific activity will no longer rise (Fig 1). This means that the sample will be effectively irradiated only to a depth of 1 mm from the surface.

The samples used have been either cylindrical (Fig 2a) or flat (Fig 2b). The boxes are made of a plastic material, usually a thin plastic foil. An aluminium envelope has also been employed (Fig 2c). This is however not practical as the aluminium is also activated and is accordingly difficult to handle. Bags made of thin plastic foil seem to be the best choice since they will not be radioactive, are easily cut open and may be discarded after use. In these packages the thickness of lithium carbonate will not exceed 2 mm. If enriched lithium (^6Li) is utilised the cross section of the carbonate will be more than ten times as large and therefore the thickness of the lithium carbonate should not exceed 0.2 mm.

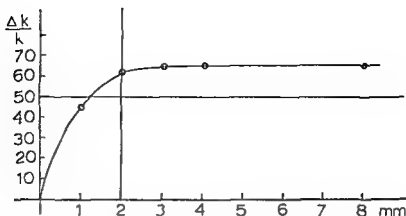


Fig. 1 Effect of thickness of sample on the reactivity of the reactor and thus on the specific activity of the sample

fectured by a chain reaction, at first ${}^6\text{Li}(n, {}^4\text{He}) {}^3\text{H}$. The resulting fast tritons ${}^3\text{H}$ will induce ${}^{18}\text{I}$ activity by ${}^{18}\text{O}({}^3\text{H}, n){}^{18}\text{I}$ (BERNSTEIN & KATZ 1953, KNIGHT et coll 1951). These two reactions are induced simply by setting some lithium salt containing oxygen in the neutron flux of a thermal reactor.

BEC & BROWN (1963) utilised Li_2O for this production. Their method is applicable for medical purposes if a modification is introduced in view of the high tritium content in the product. However, in common with many others, we have made use of Li_2CO_3 , irradiated at the Institute of Technology at Oulu in a Triga reactor with a maximum power of 100 kW. If the ${}^{18}\text{I}$ is to be without chemical and radiochemical impurities, the sample needs some chemical purification after irradiation. Known methods of distillation (ERICSSON 1961, THOMAS et coll 1965) could not be used for the separation of ${}^{18}\text{F}$ as at first the simple apparatus required for this purpose was not available. Moreover the high tritium content associated with this method (THOMAS et coll) was considered undesirable. Accordingly, with the method first applied we used Al_2O_3 as an ion exchanger (STANG 1963). This procedure appeared too slow, however at least with the chromatographic alumina at hand, wherefore the following method was thereafter employed.

Three grams of irradiated Li_2CO_3 (two hours in $4 \cdot 10^{11} \text{ n/s cm}^2$) are first dissolved in 30 ml 2.7 normal HCl . The carbonate is released and therefore the process should be carried out under a fume hood and behind lead bricks to avoid radiation hazards. The dose rate at 20 cm, without shielding, is about 20 mR/hour. One millimole of H_3PO_4 is added together with 0.2 mM of a CaCl_2 solution. The pH is adjusted to about 9 (or more) by the addition of 10 ml 2.5 normal NaOH . Calcium phosphate, carrier of the main part of the ${}^{18}\text{F}$ activity, is

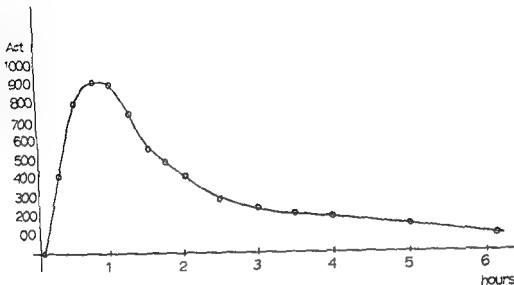


Fig 3 Blood excretion curve after an oral dose of carrier free ^{18}F fluoride

lithium. It may be assumed that under certain conditions a single dose exerts no toxic effects, but the amount could nevertheless be further reduced by a tenth by the use of isotopically enriched ^6Li lithium carbonate.

The method of purification outlined above, although not essential, has been applied because it is relatively quick and simple. After purification, only ^{18}F and ^3S isotopes are present in the final solution. Measurements have indicated, however, that some contamination with ^3H will also be present, about 1 μCi per 1 mCi of ^{18}F ingested, and lithium has therefore also been separated in this way.

Blood excretion curve and the use of ^{18}F The presence and disappearance of fluorine in the blood following its ingestion has been studied by taking blood samples within 6 hours of its oral administration (Fig 3). The disappearance attributable to radioactive disintegration has been corrected at each point so that the curve indicates only the fluorine flow to and from the blood stream. After 6 hours, no more than 10% of the maximum amount of fluorine (at 1 hour) remained in the blood. However, it cannot be expected to be excreted to this extent (BLAU et coll 1962, Dworkin et coll 1965, NUSYNOWITZ et coll 1965) which means that the fluorine must be concentrated elsewhere in the body. It is known (VAN DYKE et coll 1965, NUSYNOWITZ et coll) that fluorine con-

Table 1

Activity present in an irradiated sample of 3 g Li_2CO_3

Isotope	Activity	
^3H	2 600	μCi
^{18}F	2 000	»
^{22}Na	1 0	»
^{36}Cl	2 0	»
^{38}Cl	0 03	»
^{35}S	0 003	»
^{40}K	0 003	»

Table 2

Radiation dose due to oral administration of 1 mCi ^{18}F at 30 minutes after irradiation with no purification of sample

Isotope	Activity (μCi)	Total body (mrad)	Bone (mrad)
^3H	1 600	120	120
^{18}F	1 000	30	230
^{22}Na	0 61	1 0	1 0
^{36}Cl	0 55	0 03	0 03
^{38}Cl	0 018	0 13	0 13
^{35}S	0 002	0 02	0 01
^{40}K	0 002	0 01	0 01
Total		150 mrad	350 mrad

An increase in thickness entails a loss in the excess amount of the carbonate, without any gain of activity

Radioactive components of an irradiated Li_2CO_3 sample After irradiation and before purification, isotopes other than ^{18}F exist in the sample, dependent upon the presence of impurities in the irradiated carbonate. The most important by product is naturally tritium. Theoretically, there should be about 5 mCi of tritium to 3 g of Li_2CO_3 , although in practice much less is obtained (Table 1). This indicates that the geometry of the sample concerned is not the best possible.

Only ^{18}F and ^{22}Na peaks are detectable 24 hours after irradiation in the gamma spectrum of an irradiated sample. ^{36}Cl , which has an initial activity of 2 μCi , has a half life of 37 minutes and thus completely vanishes 24 hours after irradiation (1 60 and 2 15 MeV gammas). ^{40}K has such a slight activity that it is not discernible in the spectrum. ^3H , ^{35}S and ^{38}Cl have no gamma transitions.

Radiation dose induced by different isotopes in the sample The dose to the patient caused by the activities present when one millicurie of ^{18}F is administered and the sample is not purified, is small (Table 2). Only fluorine and tritium produce an appreciable dose. When tritium and other isotopes are separated from the fluorine, the radiation dose of ^{18}F per 1 mCi will be reduced by 35 % in bone and by 80 % in the entire body. In any event, the dose does not seem to be excessive, and for this reason the separation of tritium is not absolutely necessary. The separation of lithium which is not radioactive has been considered essential (STANG & RICHARDS 1964). Three grams of lithium carbonate contain 0 57 g

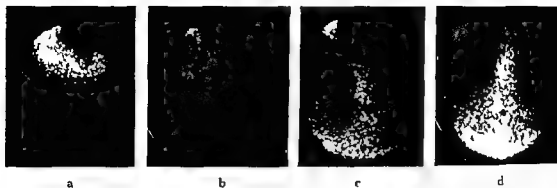


Fig. 4 Scintillation camera views from abdominal and pelvic areas demonstrating the flow of ^{18}F from stomach to spine a) At 5 min after the oral dose all the activity is still in the ventricle b) At 20 min the fluorine lies mainly in the intestine although the spine is already visible to the left c) At 50 min fluorine is seen in the middle of the lumbosacral area d) At 3 hours this is seen more clearly than in (c) The dots in (d) indicate the navel and processus ensiformis

concentrates in bone (Fig. 4). Fluorine has been used for two years for bone scanning in cases of primary or metastatic bone lesions and a report on these studies will be published.

SUMMARY

A method of producing ^{18}F for scanning primary and metastatic bone lesions is described. The ^{18}F may be prepared in the normal isotope laboratory of a clinic if the neutron irradiation can be effected at a laboratory within a distance of 20 km. Impurities and their influence upon the radiation dose are discussed. The behaviour of fluorine after its oral administration is considered.

ZUSAMMENFASSUNG

Eine Methode zur Herstellung von ^{18}F für Scanning bei primären und metastatischen Knochentumoren wird angegeben. ^{18}F kann in einem gewöhnlichen klinischen Isotopenlaboratorium hergestellt werden falls die Neutronenbestrahlung bei einem Ort stattfinden kann der nicht mehr als 20 km vom Isotopenlaboratorium entfernt ist. Beimischungen und deren Einfluss auf die Strahlendosen werden besprochen. Was mit dem Fluor nach der oralen Verabreichung geschieht wird ebenso besprochen.

RÉSUMÉ

L'auteur décrit une méthode de production de ^{18}F pour le diagnostic isotopique des lésions osseuses primitives et métastatiques. Le ^{18}F peut être préparé dans le laboratoire des isotopes normal d'un hôpital. L'irradiation par les neutrons peut être faite à une distance inférieure à 20 km. L'auteur étudie les impuretés et leur influence sur la dose d'irradiation. Il examine le devenir du fluor après son administration orale.

REFERENCES

- ANBAR M. Applications of fluorine 18 in biological studies with special reference to bone and thyroid physiology. *In* Production and use of short lived radioisotopes from reactors Vol II p 277 IAEA Vienna 1963
- BIG K. and BROWN F. Production of carrier free radio-fluorine 18 and determination of its half life. *Int J appl Rad Isotopes* 14 (1963) 137
- BERNSTEIN R. B. and KATZ J. J. Fluorine 18 properties uses. *Nucleonics* 11 (1953) 10 p 46
- BLAU M. NAGLER W. and BENDER M. A. Fluorine 18. A new isotope for bone scanning. *J Nucl Med* 3 (1962) 332
- CARLSON C. H. SINGER L. SERVICE D. H. and ARMSTRONG W. D. Preparation of carrier free radiofluoride with a new estimate of the half life of F^{18} . *Int J appl Rad Isotopes* 4 (1959) 210
- VAN DYKE D. ANGER H. O. YANO Y. and BOZZINI C. Bone blood flow shown with F^{18} and the positron camera. *Amer J Physiol* 209 (1965) 65
- DWORKIN H. J. MOON N. F. LAFLEUR P. D. and LESSARD R. J. Primary and metastatic bone tumor scanning with F^{18} . *J Nucl Med* 6 (1965) 360
- ERICSSON Y. Double labelling of sodium monofluorophosphate with P^{32} and F^{18} . *Int J appl Rad Isotopes* 10 (1961) 177
- ICRP Recommendations. See Permissible dose for internal radiation
- KNIGHT J. D. NOVEY T. B. CANNON C. V. and TURKEVICH A. Radiochemical studies. *In* The fission products Book 3 p 1916 McGraw Hill New York 1951
- NEUENOWITZ M. L. FELDMAN M. H. and MARIER J. G. A simple method of producing ^{18}F fluoride for the study of bone disease. *J Nucl Med* 6 (1965) 473
- PERMISSIBLE DOSE FOR INTERNAL RADIATION. Recommendations of the International Commission on Radiological Protection. ICRP Publication 2. Report of Committee II. Pergamon Press London 1960
- STANG JR L. G. A review of the production of special radioisotopes. *In* Production and use of short lived radioisotopes from reactors Vol I p 3 IAEA Vienna 1963
- and RICHARDS P. Tailoring the isotope to need. *Nucleonics* 22 (1964) 1 p 46
- THOMAS JR C. C. T. SONDEL J. A. and KERNS R. C. Production of carrier free fluorine 18. *Int J appl Rad Isotopes* 16 (1965) 71

✓ Book reviews

DOSIMETRIE ZUR BETATRONTHERAPIE Von Wolfgang Pohlitz 80 Seiten 55 Abbildungen
7 Tabellen Georg Thieme Verlag Stuttgart 1965 Preis 25 DM

This little book deals with the different measurements of the source of radiation and of the electron and photon beams to secure correct treatment dosimetry. These are of great topical interest in modern radiotherapy. Clinical dosimetry, including dose planning and radiation protection also have their own chapters.

Within the limited space available a good account is given of the instruments and measuring methods developed over a number of years at the Max Planck Institut für Biophysik Frankfurt am Main. A great number of practical hints on the performance of measurements and various sources of error and their avoidance are given as well as formulae and numerical data needed for converting the direct instrument readings into absolute dose values in rad. The book will be most useful to hospital physicists working with medical betatrons or other high energy accelerators but may also be read with advantage by radiotherapists.

Sven Denner

CURRENT TOPICS IN RADIATION RESEARCH Vol. 2 Edit. by M. Gbert and A. Howard \$98
pages with 118 figures and 7 tables North Holland Publishers Company, Amsterdam 1966
Price 45 guilders

In the first volume of this series the trend was predominantly radiobiologic. In the present volume some of the chapters are of a nature to demand of the reader some knowledge in physics and chemistry.

The biologic macromolecules are targets of importance in the action of radiation on living matter and it is of value to find an exposé by HENCLEIN & SCHVABEL on the radiation effects of macromolecules in general. The authors have worked with synthetic polymers and special attention has been paid to reactions in aqueous solutions rather than in the dry stage. Degradation, cross linking and gel formation of molecules as well as the effects of irradiation of varying LET's are discussed. There seem to be great variations in regard to cross linking and gel formation between various polymers depending on whether γ radiation or particle radiation is used. Energy transfer between water and dissolved polymers occurs and free radicals such as OH and H atoms add to the effects.

JUNG & ZIMMER introduce their chapter on Some chemical and biological effects of elastic nuclear collisions with the statement: "It may seem surprising to find a review article written on a topic which does not yet actually exist." This means that up to now no direct evidence of elastic nuclear collisions has been given but the authors prove their existence and suggest that such reactions give rise to biologic effects. When charged particles of high velocity are used ionization and excitation predominate and the likelihood that elastic nuclear collisions occur is very small. However at very low ion velocities more energy is dissipated by elastic collisions than by interaction between incident ions and electrons of the exposed material. Slow particles should therefore be used to prove the effect which nevertheless meets with diffi-

cultures because of their very low penetrative capacity in biologic material. The authors discuss an elegant experimental solution of the problem by means of protons and thin layers of plastic foils in which the absorption spectra produced the evidence. Work with the enzyme ribonuclease in thin layers also proved that elastic collisions between slow charged particles and this molecule caused an inactivation that increased linearly with the proton dose.

The chapter by PHILLIS on energy transport in carbohydrate is of biologic significance because of the abundance of such substance in the cells. Already in the metabolic processes energy transfer occurs in steps although not well defined in physical terms. A great number of molecules absorb light in the range of ultraviolet and visible and in biochemical processes this is followed by transfer of energy. By the application of ionizing radiation the energy becomes considerably in excess of what can be used in the biologic process. The ionizing radiation action is discussed in detail but cannot be dealt with at length in this review. In particular two carbohydrates, the d-glucos- and cyclodextrin complexes are well analysed. A chapter on the effects of ultraviolet light on photoreactivation (by JANE SETLOW) is motivated by the fact that ultraviolet has both lethal and mutagenic actions. The changes caused in nucleic acids in particular are manifold and important. The author discusses chain breaks and depolymerization, cross linking and partial denaturation. Specific reactions occur in several of the base components of the nucleic acids and DNA may lose its synthetic ability. Ultraviolet lesions can be repaired, as has been shown by many writers. This photoreactivation is in many instances promoted by heat in which reaction an enzyme seems to take part. The mechanism of ultraviolet induced mutations appears still not to be completely understood.

JOSEF MONTACCINI & MARCONI report on determinations of the initial sites of radiation effect on microorganisms, essentially *Escherichia coli* and yeast cells. Roentgen rays as well as ultraviolet rays are considered. The problem is that it usually takes several generations to detect a lethal mutation. Experiments were carried out by irradiating *E. coli* Hfr male cells (Hfr for high frequency of recombination) and mating them with non irradiated F recipient ones. During conjugation between a Hfr donor and a F recipient the genetic determinants of the donor are transferred to the zygote sequentially and in an order that is constant for a given Hfr strain. The frequency of transfer of a marker decreases as a function of its distance from the point of the chromosome first transferred, the origin O. One can thus define a gradient of transfer of the male characters and a degree of linkage between them expressed as their probability of being simultaneously transmitted to the recombinants. The study of the variation of these two factors as a result of the irradiation of the male or of the female has been used as a tool to analyse the radio-induced lethal damage. Any dominant lethal lesion induced on the male chromosome should have a lethal effect on the zygote.

BRIKMAN & LAMBERTS report on several experiments of interest in radiation therapy. The first example is on water filtration through the subepidermal layers of membranes. The permeability is greatly increased by irradiation with such small doses as 1 to 2 R and the application of moderate water pressure. This effect is counteracted by radiation protective compounds like SH groups and serotonin. The experiments have some bearing upon the penetration of activity should the situation be such that heavy fall-out occurs. Further, enzymes may be rapidly released, e.g. from erythrocytes by comparatively low doses. It is reported that ozone in low concentration has radiation sensitizing effects as demonstrated by irradiation of mice given O_3 inhalations of about 1 part per million. This treatment which has no deleterious effect as such increased the death rate considerably after a nearly lethal dose. The authors suggest that it may be worthwhile to follow up the ozone effect more in detail.

The last chapter by FOWLER on Radiation biology as applied to radiotherapy constitutes a discussion of great interest both to radiation biologists and therapists. The experimental

material on survival curves of cells or cell populations has increased considerably in the last decades, as has information on the biochemical and other factors that settle the issue of the irradiation. The author discusses cellular theories of radiosensitivity and variations due to factors such as in vivo or in vitro exposure, stage of mitotic cycle and degree of differentiation. It is not easy to recommend definite clinical procedures. He believes that the most important aspects to deal with are the anoxic cells in tumours and to find rational ways of fractionation. It is generally known that radiation sensitivity increases when cells and tissues are well oxygenated, and that in anoxia 2 to 3 times higher doses are needed for an equivalent damage. The author also points to the fact that living tumour cells are situated around capillaries whereas tissue at some distance may be necrotic. Tumour cells at the edge of necrotic regions may survive for some time however and because of the anoxic state also survive irradiation and eventually regrow. One of the main problems in radiotherapy are these anoxic and consequently resistant cells.

FOWLER considers some of the possibilities in dealing with the problems. The first of these is the application of high pressure oxygen during irradiation, as practised by Churchill Davidson and his team although many radiotherapists seem to be sceptical about this form of therapy. However six centres in the UK, at least two in USA and two in Australia are by now engaged in such treatment. The second is the breathing of 95% O_2 plus 5% CO_2 at normal pressure to afford hyperventilation and capillary dilatation and the third is local infusion of H_2O_2 which should be followed by the reaction $2H_2O + O$. Lastly radiation at high ionizing density because it kills even anoxic cells almost as well as normal cells is mentioned.

The last section is on dose fractionation in which the methods are discussed. It seems impossible to generalize or even to give preference to a particular schedule of fractionation at the present time. The author states: "There is no a priori reason why any number of fractions might be better than any other" from 2 to 200 fractions or even continuous irradiation. This drastic statement can be rephrased to mean that each therapy problem must be approached in an individual way.

Arne Forssberg

BIOPHYSIKALISCHE PROBLEME DER STRAHLENWIRKUNG Jahrestagung der Deutschen Gesellschaft für Biophysik am 23./24. April 1965 in Homburg/Saar. Herausgegeben von H. Muth. 191 Seiten mit 114 Abbildungen und 10 Tabellen. Georg Thieme Verlag Stuttgart 1966. Preis 29.70 DM.

This book of twenty six congress papers is introduced with a review of biophysics by B. Rajewsky. Some of the papers consider radiation dose calculations and the biologic actions of Thorotrast, ^{220}Ra and ^{210}Ra and their disintegration products while others deal with radiobiologic and radiochemical questions, the reactions of free radicals and their detection by electron spin resonance, radioprotective and mutagenic agents and the metabolism of ^{137}Cs . The use of analogue computers in medical and biologic research is discussed in one paper. In another paper it is pointed out that unwarranted conclusions regarding underlying mechanisms are often drawn from the shape of dose survival curves. Finally the new biophysical institute at Homburg/Saar is described.

The book should be of great interest to all active in radiation biophysics as it gives a good though necessarily somewhat disjointed account of the present state of the science as well as of work going on in West Germany. The selection of the topics was of course determined by the contributors.

Sven Benner

TELEGAMMA THERAPY OF LARYNGEAL CARCINOMA

by

O DAHL F JACOBSSON and R WALSTAM

It is now generally agreed that high energy radiation is the most convenient means of treating laryngeal carcinoma (GOLDMAN & SILVERSTONE 1960 MORRISON & DEZLEY 1962, and FLETCHER & KLEIN 1964). Various treatment units and techniques may then be advantageously applied.

Gamma radiation has been used for this purpose at Radiumhemmet for about thirty years. Teleradium units were employed until 1954. JACOBSSON (1951, 1952) reported and analysed the 1935 to 1945 material of 178 patients with carcinoma of the larynx. An intensified and more detailed individual dose planning was started in 1953. Decacurie cobalt 60 units were installed in 1954 and 1956 (LINDELL & WALSTAM 1956, DAHL, LINDELL & WALSTAM 1956); these offer better possibilities to adapt the dose distribution to the position and size of the tumour and to the anatomical conditions. From 1955 decacurie cobalt 60 was mainly used for this treatment and in recent years the simpler ordinary telecobalt therapy. The short distance gamma beam irradiation technique is suitable chiefly for small tumours; larger carcinomas or wide spread demand other techniques.

From Radiumhemmet (Acting Director: F Jacobsson) and the Institute of Radiation Physics (Director: R Walstam), Karolinska Sjukhuset, Stockholm, Sweden. Submitted for publication 4 July 1967.

material on survival curves of cells or cell populations has increased considerably in the last decades as has information on the biochemical and other factors that settle the issue of the irradiation. The author discusses cellular theories of radiosensitivity and variations due to factors such as in vivo or in vitro exposure, stage of mitotic cycle and degree of differentiation. It is not easy to recommend definite clinical procedures. He believes that the most important aspects to deal with are the anoxic cells in tumours and to find rational ways of fractionation. It is generally known that radiation sensitivity increases when cells and tissues are well oxygenated and that in anoxia 2 to 3 times higher doses are needed for an equivalent damage. The author also points to the fact that living tumour cells are situated around capillaries whereas tissue at some distance may be necrotic. Tumour cells at the edge of necrotic regions may survive for some time, however, and because of the anoxic state also survive irradiation and eventually regrow. One of the main problems in radiotherapy are these anoxic and consequently resistant cells.

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Sven Benner



Fig 2 Roentgenogram of the treatment area with magnification indicator applied to the patient's skin

Two-dimensional dose planning is performed on an anatomical plan of the cross-section through the tumour centre as illustrated in Fig 3. The choice of beam nozzles and of the distance between and angulation of the central axes of the beams is made with due regard to the size and position of the tumour and to the possible compression of soft tissues. In most patients a two-field technique with beam nozzles provided with special wedge filters has usually supplied a satisfactory dose distribution for small tumours. The height of the field has been 3, 4 or 6 cm. However, where regional metastases have been present other techniques have been used. The aim has been to deliver a calculated dose of 5 600 rad in approx. 2 to 3 weeks to small tumours and 6 000 rad in about 3 to 4 weeks to larger neoplasms. The error of method in these dose figures has been estimated to be within ± 5 and -10 per cent. The corresponding dose distribution in a sagittal section with a field height of 6 cm is given in Fig 4.

In comparison with conventional roentgen rays the hard gamma radiation gives a diminished absorption and reaction in calcified cartilage and a skin sparing effect which may also be obtained with the closed-end treatment applicators that we have used (WALSTAM 1965).

Among the special advantages of the decacurie technique may be mentioned that both the overall treatment time and the duration of the tissue reactions are relatively short. To avoid undue reactions it is of course necessary to base the dosage in the individual case on repeated clinical investigations during treatment.

Optimal results with the decacurie technique demand that the whole staff be familiar with the technique and that the setting up for each treatment is care



Fig 1 Illustration of the tracing of the anatomical outlines with the aid of a dental mould and preparation of a perspex jig



The main purpose of this paper is to present a material treated almost entirely with high energy radiation rather than to argue in favour of a special irradiation technique. Preliminary reports were given by DAHL & WALSTAM (1957) and DAHL, JACOBSSON & WALSTAM (1964). The authors feel it necessary first to give a brief summary of the technique.

The use of narrow beams from short distance gamma units with their rapid dose fall off necessitates a careful planning of the irradiation. The first step in the preparation before irradiation is illustrated in Fig 1. With the patient placed in a suitable position, the anatomical outlines of two body sections are traced with the aid of dental moulds. An individual perspex jig is prepared from these so that it is possible to bring the patient into the correct position at every treatment and also to secure accurate positioning of the beam nozzle.

A roentgenogram of the treatment area, with the flexible magnification indicator applied to the patient's skin and produced in the treatment position prescribed, is shown in Fig 2. This film is used for determination of the distance from the skin to the anterior and posterior borders of the larynx and to the spinal cord.

Table

Five year results of treatment of carcinoma of the larynx at Radonhemmet during 1953-1958

Category	Patients treated	Deaths free of cancer	Determinate cases	Symptom free	Corrected cure rate
<i>Sup glottic</i>					
T I	3	—	3	2	2/3
T II	1	—	1	—	0/1
T III	4	1	3	2	2/3
T IV	9	—	9	3	3/9
Total	17	1	16	7	7/16 (44 %)
<i>Glottic</i>					
T I	60	11	49	45	45/49
T II	24	5	19	13	13/19
T III	21	4	17	14	14/17
T IV	1	—	1	—	0/1
Total	106	20	86	72	72/86 (84 %)
<i>Total material</i>					
T I	63	11	52	47	47/52
T II	25	5	20	13	13/20
T III	25	5	20	16	16/20
T IV	10	—	10	3	3/10
Grand total	123	21	102	79	79/102 (77 %)

symptom free after 5 years because of surgery have been counted as not symptom free after 5 years. Patients who died within 6 months have been counted as dead from cancer.

The glottic carcinomas represent the largest group as there were no primary subglottic and only few supraglottic tumours in the material.

The above mentioned 1963 recommendations on clinical stage classification of malignant tumours of the larynx given by the International Union Against Cancer define only the different T, N and M categories. No proposition is made as to their combination into stages as did the corresponding 1958 recommendations. We have therefore used the T categories alone for the classification of the present material and feel that this mode of classification offers better possibilities of drawing conclusions as to the suitability of a certain treatment method for tumours differing in position and size. We further believe that it would be of value if the classification in T-categories took the mobility of the cords into

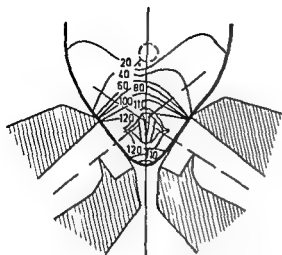


Fig 3 Dose distribution with a two field short distance cobalt technique with special wedge filters

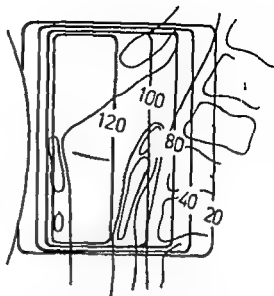


Fig 4 Dose distribution in the sagittal section with a 6 cm high field

fully controlled. It is wise in general to choose a field height of 6 cm in order to avoid subglottic recurrences. If larger tumour dimensions, more deep growth, or regional metastases are present or suspected it is advisable, when radiotherapy is chosen, always to use the kilocurie cobalt treatment techniques.

The present material dates from the year 1953 when detailed individual treatment plannings and dose calculations in carcinoma of the larynx began to be performed. It consists of 123 patients treated in the years 1953 to 1958, 114 being men (93 %) and 9 being women (7 %). Only primary cases with a histologically proven, infiltrating squamous cell carcinoma have been included. No patients have been lost to follow up. The material has been classified according to the T categories, proposed for malignant tumours of the larynx by the Committee on Clinical Stage Classification and Applied Statistics of the International Union Against Cancer in 1963. It may be mentioned that group T—I consists of tumours confined to one anatomical site within the larynx, T—II of tumours confined to one anatomical region within the larynx, T—III of tumours extending beyond one anatomical region but confined to the larynx, and T—IV, lastly, of tumours extending beyond the larynx.

The 5 year results by irradiation alone, giving the rates of cure, are presented in the Table below. Thus, patients with recurrence after irradiation, who were

REFERENCES

- CLINICAL STAGE CLASSIFICATION OF MALIGNANT TUMOURS OF THE LARYNX Intern Union against Cancer 1956
- DAHL O and WALSTAM R. Telegamma behandling av larynx cancer vid Radiumhemmet (In Swedish) Paper read at the 21st Congress of the Nordic Society for Medical Radiology Copenhagen 1957
- JACOBSSON F and WALSTAM R. Telegamma therapy of laryngeal carcinoma. *Acta Lint Cancer* 20 (1964) 1735
- LINDELL B and WALSTAM R. Der neue Telegamma Apparat des Radiumhemmets. *Sonderb. Strahlenther* 35 (1956) 253
- FLETCHER G H and KLEIN R. Dose time volume relationship in squamous cell carcinoma of the larynx. *Radiology* 82 (1964) 1032
- GOLDMAN J L and SILVERSTONE S M. The role of radiation therapy in carcinoma of the larynx. *Ann. Otol. (St Louis)* 69 (1960) 890
- JACOBSSON F. Die Ergebnisse der Strahlenbehandlung bei Larynx und Hypopharynxcarcinom am Radiumhemmet. *Arch. Ohr Nas u. Kehlk. Heilk.* 159 (1951) 97
- Teleradium treatment of laryngeal carcinoma at Radiumhemmet Stockholm. *Acta radiol.* 38 (1952) 143
- LINDELL B and WALSTAM R. A new telegamma apparatus. *Acta radiol.* 45 (1956) 236
- MORRISON R and DEELLY T J. The treatment of carcinoma of the larynx by supervoltage radiotherapy. *Clin. Radiol.* 13 (1962) 145
- WALSTAM R. Studies on therapeutic short distance and intracavitary gamma beam techniques. *Acta radiol.* (1965) Suppl. No. 236

consideration, as was the case in the 1956 recommendations. The glottic T—II group ought especially to be divided into patients with full mobility retained and patients with mobility impaired or lost, since such sub groups have a very different prognosis. We have not, however, employed any such sub division in the present case material, since the number of patients treated was considered too small. On the other hand, the presence of patients with impaired or lost mobility of the vocal cords among the glottic T—II material apparently considerably influenced the corresponding cure rate.

The 5 year cure rate for glottic carcinomas, corrected for intercurrent deaths, is 45/49 (92 %), 13/19 (68 %), and 14/17 (82 %) in groups T—I, T—II, and T—III, respectively (see table).

It appears that recurrences in patients without metastases seem to occur almost exclusively within the first three years. This fact emphasizes the importance of frequent follow up examinations during the first years after treatment.

SUMMARY

Teleradium units and from 1955 decacurie cobalt 60 units have been used for the treatment of laryngeal carcinomas. The material consists of 123 cases of primary proven infiltrating squamous cell carcinoma supraglottic in 17 and glottic in 106 patients. The 5 year irradiation cure rate for glottic carcinoma corrected for intercurrent deaths was 92.68 and 82 per cent in groups T I, T II, and T III respectively.

ZUSAMMENFASSUNG

Die Behandlung des Kehlkopfkarcinoms wurde mit Teleradium Bestrahlung und seit 1955 mit Decacurie Kobalt 60 Bestrahlung vorgenommen. Im Ganzen handelte es sich um ein Material von 123 Fällen von primären infiltrierenden Schuppenzellenkarzinom supraglottisch in 17 Fällen und intraglottisch in 106 Fällen. Nach Korrektur für dazwischen kommendes Tod zeigten die Resultate eine 5jährige Heilung in 92.68 und 82 Prozent für die Gruppen T I, T II und T III.

RÉSUMÉ

Des appareils de teleradiumtherapie et à partir de 1955 des appareils de cobalt therapie de 10—30 curie, ont été utilisés pour le traitement des cancers du larynx. Le matériel des auteurs comprend 123 cas de carcinome épidermoïde infiltrant verifié sus glottique dans 17 cas et glottique dans 106 cas. Les taux de guérison de 5 ans corrigés pour tenir compte des morts intercurrentes sont respectivement de 92.68 et 82 pour cent dans les groupes T I, T II et T III.

Effects of small radiation doses PAPE et coll described the beneficial effects of small doses of radiation and compared these to the cell destructive effects of high radiation doses. The value of the small doses and the frequency of irradiations are not important in relation to a protective mechanism. Doses over 150 R are considered harmful. The good effect of small radiation doses has in plants been found to consist of an improved tolerance to heat. The beneficial effects are manifest in animals by a quicker healing of wounds (20) and bone fractures (32-44) as well as by improved resistance against toxins (3, 36) and resistance to tumour vaccinations (16). Since the protective effect of pre-radiation with small doses is difficult to consider quantitatively PAPE chose for his investigations radiosensitive organs i.e. the spleen and testicle of the rat. He observed a faster generation of the lymphoid tissue of the spleen and of the spermatogenic function of the testis when the tissue had been pre-irradiated. His work has been confirmed by the studies of TRAUTMANN et coll. The more recent studies of DIETHELM & LORENZ under the same conditions have not confirmed PAPE's work. The reason for the contradiction in these results after radiation with small doses is not obvious. DIETHELM believes the explanation to be that the cell populations studied were not homogenous i.e. the cells in the spleen and testes were in various stages of maturation and the radiation sensitivity may therefore have been dependent on the degree of maturity.

Preradiation with large doses The influence of massive preradiation on the resistance of the organism has been studied in numerous experiments which have produced varying results. Many media (yeast, bacteria, isolated cells in vitro, small rodents, mammals) and variable criteria have been used to study the preradiation effect on the resistance to infection (1, 4, 34, 41, 43), the rate of growth of transplanted tumor cells (1, 17, 18, 39), improved tolerance to toxic drugs such as strychnine, chloroethylene, allyl alcohol (1, 15), increased exercise tolerance (7), increased mitotic activity in duodenal crypt epithelium (6) and in haematopoieses.

The effect of whole body irradiation with respect to increased resistance against the effects of a second exposure to radiation may be accurately measured by observation of the survival time. In our opinion this is best expressed as the LD_{50} dose in relation to the time interval after exposure. Some detailed references to changes in survival time in cases with prior exposure to large doses and a second radiation are cited below.

RAPER stated that an antecedent non-lethal dose of a whole body β irradiation of 3 000 rep in mice increased the LD_{50} from 4 700 rep to maximal 8 400 rep. The interval between the first and second radiation exposure was 28 to 56 days. The LD_{50} was found to be 6 700 rep from 3 days, 7 600 rep from 7 days and 8 000 rep from 14 and 112 days respectively.

ACQUIRED RADIORESISTANCE FOLLOWING WHOLE BODY IRRADIATION

by

V TAENZER and P KROKOWSKI

In experimental studies in animals, a protective mechanism following whole body irradiation has been reported upon (1, 9, 10, 11, 19, 21, 30, 31). This biologic protective mechanism has been found to be more effective and different from the well known recovery ability of the body after multiple irradiations and it will be discussed in the present paper.

It appears from a study of the literature that two contradictory facts should be considered: (1) a summation of the effects of multiple total body exposures to irradiation occurs, and (2) an adaptation of the organism similar to the experimentally proved acquired radioresistance in tumour treatment has also been observed (28, 35, 38). The present authors have in addition observed a protective mechanism that cannot be defined by these known conceptions of the response to irradiation. A special analysis of published observations in the light of our own studies has enabled us, however, to present a single scheme capable of explaining the different experimental data.

It is important to differentiate between small roentgen doses as used in the treatment of inflammatory conditions and radiation therapy in malignant conditions. In surveying the literature on radiation sensitivity one must differentiate the responses obtained with small doses (up to 25 R) from those obtained with higher (sublethal to lethal) doses.

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Preradiation with large doses The influence of massive preradiation on the resistance of the organism has been studied in numerous experiments which have produced varying results. Many media (yeast, bacteria, isolated cells, *in vitro*, small rodents, mammals) and variable criteria have been used to study the preradiation effect on the resistance to infection (1-4, 34-41, 43), the rate of growth of transplanted tumor cells (1-17, 18, 39), improved tolerance to toxic drugs such as strychnine, chloroethylene, allyl alcohol (1-15), increased exercise tolerance (7), increased mitotic activity in duodenal crypt epithelium (6) and in haematopoieses.

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In the studies of BETZ with mice, a single total exposure of 700 R was found to be lethal. If, however, the mice were first given 500 R, then the survival after a second exposure to 700 R was found to be 20 % at 7 days, 26 % at 10 days, 36 % at 15 days, and 0 % at 33 days.

KISFELY, in similar experiments with mice, found that the LD_{50} from a single exposure to radiation was 700 R. The effect of pre-irradiation with 119 R given once, twice or three times, at an interval of one week followed in two weeks by a second exposure to 700 R, resulted in survivals of 75 %, 50 %, and 17.5 %, respectively.

In a communication by DAQUISTO, the $ID_{50(10)}$ of white mice increased from 487 to 560 R after pre-irradiation with a dose of 50 R ten days before, and from 487 to 617 R when the pre-irradiation was given 17 days before.

PATTERSON *et coll.* gave mice half of the LD_{50} dose and determined the new LD_{50} dose after different time intervals with increasing doses of whole body irradiation. During a time interval of two days, the LD_{50} was reduced from 518 to 493 R. With a longer interval from 10 to 20 days between the first and second irradiation, the new LD_{50} was increased from 728 to 799 R. In a similar study in the rhesus monkey (30), it was shown that 20 days whole body irradiation with 200 R the LD_{50} increased from 570 to 623 R.

SAKKA & HAMATA irradiated a group of mice with $1/2 LD_{50}$ ($= 350$ R) which a week later gave a LD_{50} of 480 R. Only 37 % of the animals died. A second group of animals, under equal conditions, were given $1/2 LD_{50}$ with the sieve method, and in these animals the mortality was only 33.5 %. The result seems to underline the advantages of the sieve method.

Analogous observations of a diminished mortality rate due to pre-irradiation were reported by DIMITROW, and by GRAEVSKAJA & KEJINA in experiments in dogs.

BRAUN, and numerous other authors (6, 20, 22) were on the other hand unable to confirm that pre-irradiation had any beneficial effect on survival following a second dose of radiation. Rats, which were irradiated with doses of 200, 350, and 500 R, during time intervals of 4, 6, and 10 days before a lethal dose, died earlier than controls that were irradiated only with the lethal dose.

We have in our experiments found a significantly decreased effectiveness of a second exposure to radiation in rats earlier irradiated with large doses. A pre-irradiation of 750 R with the sieve method raised the $LD_{0.50(10)}$ following the second exposure to radiation without a sieve, from 925 R to 1850 R after a time interval of half a year. In another study, we also gave the second radiation exposure dose with a sieve: the $LD_{50(10)}$ was then raised from 1950 R to 3000 R. Detailed information about these experiments has been published earlier (40).

The influence of the time interval between two irradiations upon the increase in radiation sensitivity can be comparatively easily recognized. Time intervals of irradiation from several hours to a few days lead to a summation of the radiation hazards. Prolongation of the time interval between irradiations leads after an indifferent phase to a decrease in the radiation sensitivity for long time intervals (> 10 days).

The size of the dose of preradiation is equally important. The observations reported in the literature vary with the age, sex and race of the animals irradiated, as well as with the quality of the radiation used, and on the evaluation of the effect observed. The recovery periods are reported to be faster in primates than in rodents, faster in mice and rats than in guinea pigs, and to be especially slow in amphibians (30). An additional difficulty lies in the sometimes reported fractionation of the preradiation.

In our analysis of the dose/time/effect relations we only took account of those observations in the literature in which the preradiation had been given in a single dose and in which the biologic effect was clearly measurable. Race, age and sex could be neglected since only the LD_{50} was evaluated, which is characteristic for each race and genotype.

In summarizing the observations all the doses applied were considered as fractions of the characteristic LD_{50} from each race. This LD_{50} was used, and it was compared to the LD_{50} of observations without any preradiation, i.e.

$$\frac{\text{radiation effect (LD}_{50}\text{) with preradiation}}{\text{radiation effect (LD}_{50}\text{) without preradiation}}$$

A value less than one in this scheme means that because of a partial summation of radiation effects the LD_{50} is decreased after a second irradiation. Values above one indicate the protection effect of a second radiation dose in pre-irradiated animals. If the results are standardized in the way described above and put in a three dimensional coordinate system in which the ground area represents the dose applied (fraction of the LD_{50}) and the time interval between the first and second irradiation, and in which the length of the columns expresses the effectiveness of a second radiation, a dose-time/effect scheme is obtained (see the accompanying figure). In considering this scheme it is feasible to outline the limits in which the protective mechanism after a second radiation becomes effective.

Influence of the time interval During the first days following radiation the radiation sensitivity is diminished. With prolongation of the time interval between the first and second irradiations the organism recovers and the endurance of

radiation enhances slowly. Around the 8th to 10th day a period with clearly improved radioresistance is then recognizable and lasts at least 200 days.

Influence of the size of the preradiation dose Small doses of primary radiation (below 5 % of the LD₅₀) release no protective effect. This effect becomes obvious when the primary radiation dose is higher than 10 % of the LD₅₀. In cases in which the preradiation exceeds 80 % of the LD₅₀, the protective mechanism does not develop.

This dose/time effect scheme indicates that the varying observations in the literature may be evaluated from one standpoint. An enhanced radioresistance will not occur if the time interval between the first and second radiation doses is too short or if the dose of the primary radiation is too high or too low.

Mechanism leading to improved radioresistance Each dose of radiation results in an unspecific stimulation of the organism. The reaction of the organism is determined by the hypophyseal-adrenal system and promotes an increase in dynamics. The favorable effect of small radiation doses may be understood by the adaptation of the organism in this sense. Large doses of radiation overcome the effect which becomes unimportant since cell destruction promotes different ways of reaction of the organism, i.e. denaturation of protein which leads to an antigen-antibody reaction and to the development of complement-binding antibodies. Changes in the immunologic pattern of the organism after irradiation were suggested by the observation that the blood of irradiated animals releases a protective effect against radiation in other animals in which transfusion has taken place.

Furthermore, characteristic changes in serum protein electrophoresis have been reported with an augmentation of antibody-transferring gamma globulin at 10 days after irradiation, i.e. at the beginning of the phase of raised radioresistance. KISELEV et coll. (1956) succeeded in directly demonstrating the complement-binding antibody. The antibodies are demonstrable for three to four months, which is about the length of time of the increased radioresistance. The titres of the antibodies and the radioresistance follow an almost parallel decline. Multiple pre-irradiations and too high single radiation doses damage the antibody-producing R&S and the antibody-building ability is thus diminished in spite of large protein denaturation. On the other hand, doses that are too small do not allow protein denaturation and antibody production.

Further experiments will be needed for a better understanding of the mechanisms of protection development after irradiation which are still known only to a small extent.

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Further experiments will be needed for a better understanding of the mechanisms of protection development after irradiation, which are still known only to a small extent.

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SUMMARY

The investigation has demonstrated that each whole body irradiation of animals influences the dose/effect relation of a second irradiation. The data indicate that a protective mechanism correlates to the primary dose applied and to the time interval. Only under special circumstances did whole body irradiation promote protection against a second irradiation.

ZUSAMMENFASSUNG

Jede Ganzkörperbestrahlung beeinflusst die Beziehung, Dosis/Effekt einer folgenden zweiten Bestrahlung. Die Analyse tierexperimenteller Ergebnisse zeigt, dass die Ausbildung eines Schutzmechanismus von der Höhe der Vorbestrahlungsdosis und dem Zeitintervall zwischen beiden Strahlenexpositionen abhängt. Nur unter bestimmten Voraussetzungen kann eine Ganzkörperbestrahlung vor einer zweiten Bestrahlung schützen.

RÉSUMÉ

Cette expérimentation montre que chaque irradiation de tout le corps d'animaux influence sur le rapport dose/effet d'une seconde irradiation. Les résultats des expériences montrent que le mécanisme protecteur est lié à la première dose appliquée et à l'intervalle de temps. C'est seulement dans des circonstances spéciales que l'irradiation de tout le corps confère une protection contre une seconde irradiation.

REFERENCES

1. ALEXANDROW S. N. und GALROVSKAJA K. T. Über die Änderung der Radioresistenz des bestrahlten Organismus. *Med. Radiol. (Mosk.)* 4 (1959) 15.
2. BETZ H. Sur l'importance de la phase de résistance de l'organisme lors de l'application d'une dose létale de rayons X. *C. R. Soc. Biol.* 144 (1950) 1439.
3. BIRKNER R., MEYER R. D. und TRAUTMANN J. Über Röntgenkleindosenwirkungen auf experimentell mit *Bacterium pneumoniae* Friedländer gesetzte Septikämien. II. Mitteilung: Der Einfluss kleindosiger Röntgenganzbestrahlungen vor einer subkutanen Infektion (Vorbestrahlung). *Strahlentherapie* 103 (1957) 552.
4. BIGGARD J. D., HUNT H. B., NEFLY O. A. and SCOTT I. Experimental studies of the mechanism of action of X-ray therapy upon infection. *Radiology* 39 (1942) 691.
5. — — — — The mechanism of action of roentgen therapy upon infection. *Ann. Surg.* 115 (1942) 996.

- 6 BLOOM M A : Acquired radioresistance of the crypt epithelium of the duodenum
Radiology 55 (1950) 104
- 7 BRAUN H : Experimentelle Untersuchungen über die Wirkung von Röntgenganz-
bestrahlungen auf den tierischen Organismus bei nachfolgender Bestrahlung mit
Letaldosen Oncologia (Basel) 10 (1957) 272
- 8 — Über die Steigerung der Leistungsfähigkeit der Ratten nach Ganzkörperbestrahlung
geprüft im Schwimmversuch Strahlentherapie 119 (1967) 462
- 9 CRONKITE E P, SIPE C, R, ELTZHOLTZ D C et coll : Increased tolerance of mice to
lethal X radiation as a result of previous sublethal exposures Proc Soc exp Biol
73 (1950) 184
- 10 DAQUILISTO M P : Acquired radioresistance Radiat Res 10 (1959) 118
- 11 DIMITROV A : Beitrag zur Frage der Immunität gegen ionisierende Strahlen Strahlen-
therapie 104 (1957) 436
- 12 — Untersuchungen an Tieren mit Immunität gegen ionisierende Strahlen Strah-
lentherapie 124 (1964) 114
- 13 DIETHELM L und LORENZ W : Über Unterschiede in der Reparation der strahlenge-
schädigten Rattenmilz Eine histologische und zytologische Studie am 7. und 8. Tag
nach 600 R — Röntgen Ganzkörperbestrahlung und zehntägiger Vorbestrahlung
mit täglich 3 R Strahlentherapie 122 (1963) 222
- 14 — — Über Unterschiede des strahlengeschädigten Rattenhodens Strahlentherapie 123
(1964) 207
- 15 EGER W und TERRLICH CH : Körperganzbestrahlung und Allylkoholschädigung der
Leber Ein Beitrag zur Resistenzänderung des Organismus durch Röntgenbestrahlung
Strahlentherapie 105 (1958) 296
- 16 FALK H : Die Wirkung kleinster Dosen von Röntgenstrahlen auf das Ascites Carcinom
der Maus und seine Abwehr Strahlentherapie 98 (1955) 518
- 17 FRANKL O und KIMBALL C P : Über die Beeinflussung von Maus-tumoren durch Rönt-
genstrahlen Wien klin Wschr (1914) 1448
- 18 GOLDSTEIN L M : Diss Leningrad 1941 Cited by F GAUWERKY und F HEINZEL in
Fortschr Röntgenstr 95 (1961) 299
- 19 GRAEVSKAJA B M und KEJLINA R J : Die Herabsetzung der Empfindlichkeit von
Tieren gegen Einwirkung von Röntgenstrahlen in letaler Dosis bei ihrer vorherge-
henden Bestrahlung mit nicht letalen Dosen Biofizika 1 (1956) 230
- 20 HEITE H J und TENISAEFF D : Zur Schutzwirkung kleiner Röntgendosen gegenüber
nachfolgender Massivbestrahlung Strahlentherapie 103 (1957) 115
- 21 KISELEV P N, BLISINI P A und NIKITINA K I : Immunologische Analyse des Zustandes
einer erhöhten Resistenz des Organismus gegen ionisierende Strahlen Med Radiol
(Mosk) 1 (1956) 43
- 22 KREBS A F and STORER J B : Adaption to ionizing radiation U S Army Medical
report 175 Fort Knox Kentucky 1955
- 23 KROKOWSKI E und TAENZER V : Der radiogene Strahlenschutzeffekt Strahlentherapie
130 (1966) 139
- 24 LANCENDORFF H : Über die Beeinflussbarkeit strahlenbedingter biologischer Reaktionen
durch chemische Substanzen Strahlentherapie 85 (1951) 391
- 25 — Das Problem des Reaktionsvorganges bei der biologischen Strahlenwirkung Strahlen-
therapie 88 (1952) 164
- 26 MOLE R H : Quantitative observations on recovery from whole body irradiation in
mice Brit J Radiol 29 (1956) 563

- 27 — NEAL I I and NEARY A J Quantitative studies on recovery from whole body irradiation in mice *Brit J Radiol* 32 (1959), 483
- 28 MOTTRAM J C On the relationship between β and γ radiation in the treatment of tumors *Brit J Radiol* 5 (1932), 768
- 29 PAPE R and JELLINKE N Important variations in the organic findings after total and local radiation and the particular effects of small scale dosages The spleen as a test for various radiation effects *Radiol Austriaca* 3 (1950) 43
- 30 PATERSON E GILBERT C W and HAIGH M Effects of paired doses of whole body irradiation in the rhesus monkey *Brit J Radiol* 29 (1956) 218
- 31 — — and MATTHEWS J Time intensity factors and whole body irradiation *Brit J Radiol* 25 (1952) 427
- 32 POBEDINSKIY M N Reaktionen des Knochengewebes auf Bestrahlung mit Röntgenstrahlen und radioaktiven Substanzen *Vestnik chir* 76 (1955) 116
- 33 RAPER J R Effects of total surface beta irradiation *Radiology* 49 (1947) 314
- 34 ROWE W P Protective effect of pre irradiation on lymphocytic choriomeningitis infection in mice *Proc Soc exp Biol* 92 (1956) 194
- 35 RUSS S Experimental studies upon lethal doses of γ rays and radium for human and other tumors *Brit J Radiol* 29 (1924) 275
- 36 SACHER G A On the statistical nature of mortality with especial reference to chronic radiation mortality *Radiology* 67 (1956) 250
- 37 SAKKA M and KAMATA R An increase in tolerance in mice by field fractionated (sieve) γ irradiation *Radiation Res* 9 (1958) 341
- 38 SNELLMAN H Attempt to develop reduced radio sensitivity in Jensen rat sarcoma by means of roentgen irradiation *Acta radiol* 16 (1935) 545
- 39 STENSTROM K W VERNUND H MOSSER D G and MARVIN J F Effects of roentgen irradiation on the tumor bed I The inhibiting action of local pretransplantation roentgen irradiation (1500 R) on the growth of mouse mammary carcinoma *Radiat Res* 2 (1955) 180
- 40 TAENZER V und KROKOWSKI E Änderung der Radiosensibilität durch Vorbestrahlung Strahlentherapie 129 (1966) 1
- 41 TALIAFERRO W H and TALIAFERRO L G Effects of γ rays on immunity A review *J Immunol* 66 (1951) 181
- 42 TRAUTMANN J FREY J G und SCHAAF J Experimentelle Untersuchungen über die Wirkung kleinster Röntgendosen auf das Keimepithel des Rattenhodens *Strahlentherapie* 91 (1953) 602
- 43 WARREN S and DUNLAP C E Effects of radiation on normal tissues III Effects of radiation on the blood and the hemopoietic tissues including the spleen thymus and lymph nodes *Arch Path* 34 (1912) 562
- 44 ZEMLJANYOY A G Über die Heilung von Knochenbrüchen und die Verteilung von radioaktivem Phosphor im Knochen callus nach vorheriger Ganzbestrahlung der Versuchstiere *Vestnik chir* 77 (1956) 59

RENOGRAPHIC ANALYSES IN RADIATION THERAPY OF CARCINOMA OF THE UTERUS

by

M BRITES PATRÍCIO and A M BAPTISTA

An examination with radioisotopes is a simple and practical means of separately determining the function of the kidneys. The method was first proposed in 1956 for the study of renal disease and hypertension and consists of the intravenous introduction of a radioactive material with selective renal excretion. VORDYKE (1960) utilized hippuran labelled with ^{131}I for the first time and proved its superiority to substances previously employed. RODDICK, GIBBIE & FLANAGAN (1964) studied urinary tract disfunction associated with gynecologic operations. DISCHE (1963) on isotope examination of cervical carcinoma cases found that 50% of 90 cases studied more than three months after treatment were abnormal and 30% of 17 new cases had delayed drainage. RODDICK et coll reported the results of an investigation of 26 gynecologic cases all of which were subjected to radiotherapy. MELDOLE et coll (1964) published the results of an isotope examination in 21 cases of carcinoma of the uterus and reported an incidence of urinary tract complications in 57% of the

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Table 1

Results of isotope examinations before irradiation in 141 cases of carcinoma of the uterus

Stage	Number of cases	Per cent of cases	Normal findings		Abnormal findings				
			No	°	Unilateral alteration			Bilateral alteration	
					Right	Left	°	No	°
II	29	20.5	15	51.7	3	3	20.8	8	27.5
III	61	63.3	10	16.4	12	1	21.3	38	62.3
IV	17	12.1	3	17.6	—	3	17.6	11	64.8
Postoperative	34	24.1	20	58.8	2	1	8.8	11	32.4
Total	141	100	48	34.2	17	8	17.5	68	48.3

cases DEWULF et coll (1964) were of the opinion that this test was more sensitive than urography and gave indications of stasis when urography still gave strictly normal findings.

All of these authors pointed out the great advantages of the radioisotope function test for the study of the urologic conditions in gynecologic cases, because of its sensitivity, high tolerance, great simplicity and easy reproducibility.

The study of 141 cases of carcinoma of the uterus, in which the present authors have carried out 257 isotope examinations before and after gamma radiation therapy, are presented in this communication.

Material and Method All patients fast for 12 hours prior to the study. The kidneys are localized with an intravenous injection of chloromerodrin labelled with ^{203}Hg (1 μCi) (Radiochemical Center, Amersham, England) administered 20 minutes before beginning the examination. The posterior surface of each kidney is identified by careful positioning of a large angle collimated scintillation probe until the points of maximal radioactivity are observed, with patient in prone position. Thereafter 0.5 μCi per kg bodyweight of sodium iodohippurate, labelled with ^{131}I , according to the technique used by MITTA FRAGA & VEALL (1961) and by CEIA, LIMA & BAPTISTA (1965) are injected into an antecubital vein. The radioactivity, as detected by the scintillation detector, is registered with a recorder coupled to a ratemeter.

A prolonged uninterrupted accumulation of the radionuclide occurs whenever there are alterations in the outflow of the urinary tract, as often happens in advanced stages of carcinoma of the cervix. This is reflected by a

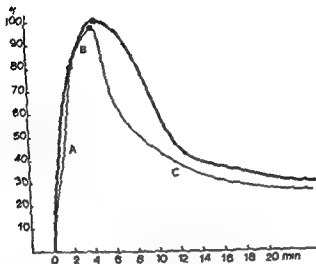


Fig. 1 Bilaterally normal isotope examination in a case of carcinoma of the cervix stage II. Labelling of curve components: A — initial spike; B — accumulation phase (secretion of function segment); C — excretory phase.

continuously rising tracing is related with eventual complete obstruction of the urinary tract. The excretory phase is very slow when there is incomplete obstruction. Considerably prolonged complete or incomplete obstruction leads to a secondary alteration of the renal parenchyma indicating hypofunctioning or absence of kidney and the renogram is characterized by a low level vascular peak which is followed by a plateau. We obtained 257 renograms in our 141 cases of carcinoma of the uterus. The cases were divided into four groups:

- | | |
|--|----------|
| 1 Carcinoma of the cervix stage II | 29 cases |
| 2 Carcinoma of the cervix stage III | 61 cases |
| 3 Carcinoma of the cervix stage IV | 17 cases |
| 4 Adenocarcinoma of the corpus uteri operated upon | 34 cases |

Renograms were obtained prior to gamma therapy in all the cases and in 74 cases the examination was repeated after treatment in some cases more than once.

The patients were treated by cobalt teletherapy or cesium teletherapy with the technique of four fixed fields or with a pendular technique. The tumour dose varied from 4 000 rad to 7 000 rad administered during four to seven weeks. In some cases the external radiation was followed by curie therapy so

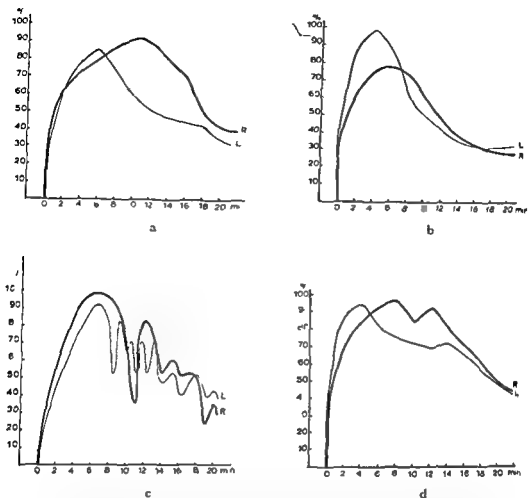


Fig 2 Case 1 Isotope examinations a) Renogram before gamma therapy Incomplete obstruction on the right side b) About 2 months later in the middle of the treatment period Total recovery c) Renogram obtained immediately after curie therapy Intermittent outflow oscillations d) Ten days after radiotherapy Marked bilateral obstruction

that the combination of radium and telegamma therapy was calculated to deliver approximately 11 000 rad to point A and just less than 5 000 rad to point B These points are the ones usually considered in curie therapy

Results

A greater frequency of invasion of the left parametrium was observed in 107 cases of carcinoma of the cervix

The results of the renographic examinations before radiotherapy are given in Table 1 Of the 29 cases in stage II, 51.7% were of normal appearance,

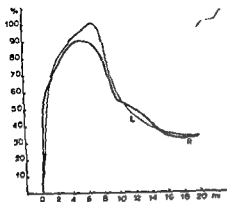


Fig 3 Case 1 Renogram obtained six months after treatment. The appearances are normal.

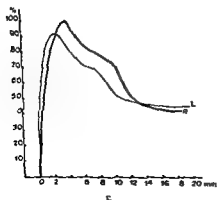
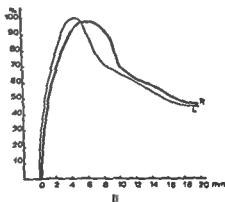
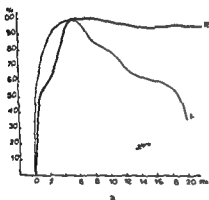


Fig 4 Case 2 Isotope examinations: a) Renogram obtained before irradiation. Total obstruction on the right and partial obstruction on the left side. b) After cesium teletherapy. Total recovery. c) Three months after treatment. Normal appearances.

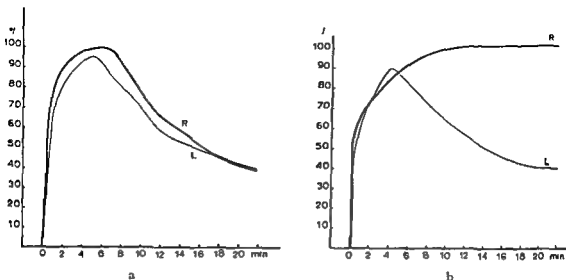


Fig 5 Case 2 Isotope examinations a) Six months after treatment Normal appearances b) Last test performed nine months after treatment revealed marked obstruction on the right side (The gynecologic examination disclosed recurrence)

20.8 % had unilateral alterations, and 27.5 % had bilateral alterations. Of the 61 cases in stage III, 16.4 % were of normal appearance, 21.3 % had unilateral and 62.3 % bilateral alterations. Of the 17 cases in stage IV, 17.6 % had normal signs, 17.6 % had unilateral and 64.8 % bilateral alterations. Of the 34 cases operated upon, 58.8 % had no changes, 8.8 % had unilateral and 32.4 % bilateral alterations.

It is evident that the right kidney is the more frequently disturbed in cases with unilateral alterations. Considering all the cases, 93 (66 %) had abnormal, and 48 (34 %) normal renograms (Fig 1). Repeat examination after radiotherapy was performed in 74 cases, a few of which are presented below.

Case reports

Case 1 Stage II This was abnormal before gamma therapy (incomplete obstruction on the right side). Examination in the middle of the treatment indicated recovery. Outflow oscillations in relation to marked peristaltic waves were observed immediately after curie therapy. Ten days after radiotherapy a further test disclosed marked bilateral obstruction (Fig 2). Six months later the test (Fig 3) and the gynecologic examination were negative.

Case 2 Stage IV On examination before irradiation total obstruction on the right and partial obstruction on the left side were demonstrated (Fig 4a). A further test immediately after cesium teletherapy indicated total recovery (Fig 4b). Examinations performed three (Fig 4c) and six months later (Fig 5a) showed normal conditions. The last test performed nine months later (Fig 5b) revealed marked obstruction on the right side and the gynecologic examination suggested recurrence.

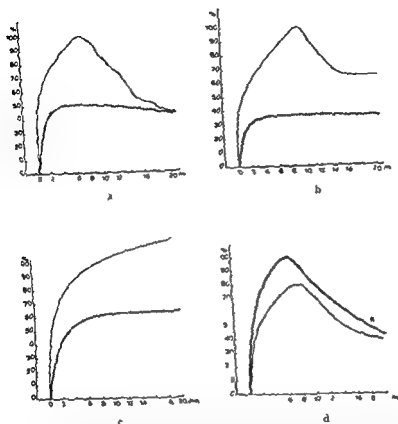


Fig 6 Case 3 Isotope examinations a) Before treatment Outflow obstruction and diminution of function of right kidney b) Immediately after radiotherapy c) About a month after radiotherapy Abnormal appearances d) One year later Normal sign

Case 7 Stage III Diminution of function on the right side Two tests performed after radiotherapy both revealed deterioration One year later the appearances were normal and the patient was well Cytologic investigation was negative (Fig 6)

A summary of the results of repeat examination, before and after irradiation in the 74 cases is presented in Table 2 In 12.2% of these the appearances returned to normal in 22.9% partial recovery took place and in 4.1% slight recovery was noted There was no improvement in 24.3% deterioration in 14.9% and 21.6% remained normal

A correlation is presented in Table 3 between the clinical course and the findings in isotope examinations in 61 cases of carcinoma of the cervix

Table 2

Summary of results in 74 cases with repeat examination before and after irradiation

		Stage II		Stage III		Stage IV		Post operative		Total	
		No	%	No	%	No	%	No	%	No	%
Recovery	Total	4	21.1	3	9.1	—	—	2	15.4	9	12.2
	Partial	3	15.8	11	33.3	2	22.2	1	7.7	17	22.9
	Slight	—	—	2	6	1	11.1	—	—	3	4.1
Without improvement		6 N	47.4	6 N	18.2	1 N	11.1 N	3 N	46.1	16 N	21.6 N
		3 P		8 I	24.3	4 P	44.5 P	3 P		18 P	24.3 P
Deterioration		3	25.7	3	9.1	1	11.1	2 N	30.8	11	14.9
								2 I			
Total		19	25.7	33	44.6	9	12.2	13	17.5	74	100

Discussion

The results indicate the high frequency of urologic complications in carcinoma of the uterus. We could not say, however, to what extent the inflammatory alterations of the parametrium were responsible for the complications. The examination with hippuran ¹³¹I is an effective method of demonstrating urinary tract abnormalities resulting from gynecologic disturbances; it is simple to perform, is well tolerated by the patient, and in practice presents no contra indications. Its use would therefore appear justified in all cases of carcinoma of the uterus.

Abnormal appearances do not necessarily indicate the site of an obstruction, however, and it is often advisable to follow up with urography. The isotope examination is not meant to replace urography but to supplement it. It certainly constitutes an alternative in the long term follow up of cases of carcinoma of the uterus, since it is readily available, is better tolerated, costs less and is a highly sensitive test.

It appears that a normal isotope examination is of good prognostic value. All cases except one in stage II were well and without recurrence one year after treatment. Of the six cases in stage III, five were well and without recurrence, and only one case was without improvement 14 months later. One case in stage IV was well one year later.

The results also demonstrate that the isotope examination is valuable. It supplements the findings of the clinical examination with respect to invasion.

Table 3

Renographic findings in relation to the clinical progress

Stage	Number of cases	Alive		Dead	Lost	Months of observation		
		With lesions	Without lesions			0-6	6-12	12-24
Normal appearances before irradiation (21)	II	6	1	4	—	1	3	1
	III	6	1	5	—	—	2	2
	IV	1	—	1	—	—	—	1
Total recovery (11)	II	4	1	3	—	—	1	1
	III	3	1	2	—	—	—	3
	IV	—	—	—	—	—	—	—
Partially improved (31)	II	3	1	1	—	1	2	—
	III	13	3	4	—	2	10	2
	IV	3	2	1	—	3	—	—
Abnormal appearances without improvement after irradiation (25)	II	3	1	—	—	—	2	1
	III	8	2	2	1	3	5	2
	IV	4	2	—	—	2	3	—
Deterioration after irradiation (7)	II	1	1	—	—	—	—	1
	III	2	2	—	—	—	—	2
	IV	1	1	—	—	1	—	—
Normal appearances before irradiation and abnormal after irradiation (3)	II	2	1	—	—	1	1	—
	III	1	—	—	—	1	—	—
	IV	—	—	—	—	—	—	—

of the parametrium and allows an evaluation of the irradiation effect in gynecologic cases

We could not ascertain to what extent the deterioration indicated by the renogram may have been due to oedema. One case with an abnormal isotope examination immediately after the treatment showed no abnormal features two months later. In another case total recovery was recorded in the middle of the treatment period while at its termination the examination disclosed bilateral obstruction. Six months later the appearances were again normal.

Continuation of the abnormal appearances at the isotope examinations is a bad prognostic sign although it would seem as if ureteral stasis may exist without any indication of recurrent or persistent disease. This was observed

in a woman with carcinoma of the cervix, stage III, in whom the follow up examinations after gamma therapy indicated deterioration. This patient was well, though clinically induration of the parametrium was observed. The histologic analysis was negative. The signs of deterioration must be attributed exclusively to irradiation fibrosis.

We feel that it is of great value to perform isotope examinations not only during the follow up cases of carcinoma of the uterus treated with ionising radiation but also in all gynecologic cases before beginning any treatment, this because of the prognostic importance related to the knowledge of any eventual abnormality of the urinary tract.

SUMMARY

In 141 cases of carcinoma of the uterus 257 isotope examinations of the kidneys with hippuran ^{131}I were performed before and/or after radiotherapy. The results revealed that these tests are useful for demonstrating invasion of the parametrium and allow objective evaluation of the therapeutic effect of irradiation in gynecologic cases.

ZUSAMMENFASSUNG

An 141 Fällen von Uteruskarzinom wurden 257 Isotopen Untersuchungen der Nierenfunktion mit Hippuran ^{131}I bevor und/oder nach Strahlentherapie vorgenommen. Die Resultate zeigten, dass solche Untersuchungen sehr wertvoll sind, um eine Invasion des Parametrium zu entdecken und um den Erfolg der Strahlentherapie zu beurteilen.

RÉSUMÉ

Les auteurs ont fait deux cinquante sept examens isotopiques des reins avec l'hippuran ^{131}I dans 141 cas de cancer de l'utérus où il y avait une indication clinique de radiothérapie. Les résultats ont montré que ces examens sont utiles pour mettre en évidence l'invasion du parametrium et pour permettre de juger objectivement l'effet thérapeutique de l'irradiation dans les affections gynécologiques.

REFERENCES

- BURNS II C, FAYRETT H S and BRACK C II: Value of urologic study in management of carcinoma of cervix. *Amer J Obstet Gynec* 80 (1960) 997.
- CEJA M, LIMA M M and BAPTISTA A M: I reparação e análise cromatográfica do hipurano marcado. *Arch Pat* 37 (1965) 75.
- DEWULF L, THIERY M, VAN VAERENBERGH P M et VANDEKERCKHOVE D: Le néphrogramme isotopique en gynécologie. *Bull Soc belge roy Gynéc Obstét* 4 (1964) 243.
- DISCHF S, CAPLAN L and KRAMER S: The isotope renogram in carcinoma of the cervix. A preliminary report. *Amer J Roentgenol* 90 (1963) 149.

- GIARELLI S DAMICO GRATTAROLA et coll. Risultati preliminari della renografia nelle complicazioni urologiche del carcinoma del collo dell'utero Tumori 51 (1965) 39
- MELDOLESI V TAROLO G L PASSERE R and SINIGAGLIA A L'interesse offerto dalla radio-renografia nella diagnosi delle complicazioni urologiche di affezioni ginecologiche Minerva urol 16 (1964) 157
- MITTA A E A FRAGA A and VEALL N A simplified method for preparing ¹³¹I labelled hippuran Int J appl Radiat 12 (1961) 146
- NORDYKE R A Use of radioiodinated hippuran for individual kidney function test J Lab clin Med 3 (1960) 56
- RIHAMY R and STANDER R Pyelographic analysis of radiation therapy in carcinoma of the cervix Amer J Roentgenol 87 (1962) 41
- RODDICH J W GERBIE A B and FLANAGAN G L The use of the radioisotope renogram in the follow up of treated gynecologic malignancy Amer J Obstet Gynec 88 (1964) 97
- SCLACIO G SAVIGNONI R e SEMPREBENE L La funzione renale in corso di affezioni ginecologiche Possibilita di impiego della methodica renografica con radiohippuran Acta isot 4 (1964) 269
- WINTER C C A clinical study of a new renal function test J Urol 76 (1956) 187

ABSORPTION OF ^{210}Pb FROM THE GASTROINTESTINAL TRACT OF MAN

by

JOHN B. HURSH and JORMA SUOMELA

For the calculation of radiation hazard from ingestion of lead isotopes it is necessary to specify the fractional amount which is absorbed from the gastrointestinal tract. The ICRP 1959 Report lists a value of 8 per cent based on experiments with stable lead. Because of the possibility that carrier free lead of high specific radioactivity might behave differently, ^{210}Pb , the 106 hour half life daughter of thoron, was administered to four volunteer subjects. Subject A received one oral and one intravenous dose, subjects B and C each received a single oral dose, and subject D received a single intravenous dose. Based on the fractional amount excreted in the urine after intravenous injection it was estimated that absorptions of 13, 81, and 16 per cent had occurred when ^{210}Pb was taken by mouth.

Preparation of dose The ^{210}Pb dose for oral consumption was prepared by passing a stream of 50 per cent O_2 - 50 % CO_2 through a 0.7 mCi . The

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stearate, filter cartridge source (HURSH & LOVLAAS) sweeping the released thoron gas through a fritted glass bubbler stuck into 250 ml of beer at a gas flow rate of 50 ml per min. The beer was contained in a 2 liter glass bottle. Recovery of ^{210}Pb using beer as the vehicle was superior to recovery using coca cola weak ascorbic acid solution or physiologic saline. It was assumed that the foam generated by the bubbling process tended to hold the 55.6 s half life thoron captive until decay occurred. Although the end product was somewhat flat the subjects found it palatable. The period of thoron flow was adjusted so as to provide a ^{210}Pb activity equal to about $5\mu\text{Ci}$ at the time of ingestion. A delay of > 10 hours was introduced between preparation and ingestion to ensure transient equilibrium between ^{210}Pb and its 60.5 min half life ^{210}Bi daughter.

A similar method was used to prepare the intravenous dose except that 20 ml of physiologic saline in a 1 liter plastic bottle was used as the vehicle. Subsequently the saline solution containing ^{210}Pb was transferred to a silicone coated penicillin bottle for sterilization prior to the injection of 10 ml (about $1\mu\text{Ci}$ ^{210}Pb) into the antecubital vein.

In all cases gamma measurement of the preparation bottles, plastic syringes or drinking vessels and transfer vessels showed that delivery of dose was better than 99 per cent complete. Aliquots of the dose were routinely set aside for later verification.

Doses were administered 1 to 2 hours after a light breakfast.

Sample collection and measurement The subjects saved all urine and feces voided until the radioactive content decreased below the sensitivity of the counting method. Collection was made directly into 1 liter plastic cartons. The samples were measured for gamma activity by placing the collection carton on the upper surface of a 10 cm diameter, 10 cm thick NaI(Tl) crystal detector surrounded by a shielded compartment. The phototube output was fed into the first quarter of a 512 channel spectrum analyzer calibrated to 16 keV per channel. The ^{210}Pb band was taken from 0 to 0.4 MeV and the ^{210}Bi band from 0.416 to 2.00 MeV. Calibration constants were established by measuring freshly prepared standardized ^{210}Pb solutions at intervals during the growth of ^{210}Bi and by including a solution volume range equivalent to that of the samples. These data enabled calculation of the correction factor to be applied to the counts in the ^{210}Pb band to take account of the Compton contribution from the ^{210}Bi gammas. For example given a urine sample of 200 ml the conversion constant for ^{210}Pb was 195 cpm per nCi and for ^{210}Bi was 130 cpm per nCi. The Compton correction was 0.87 times the cpm in the ^{210}Bi band. Backgrounds were about 350 cpm for the ^{210}Pb band and 215 cpm for the ^{210}Bi band. Counting times were 20 to 40 min per sample. Sample volumes were estimated by weighing.

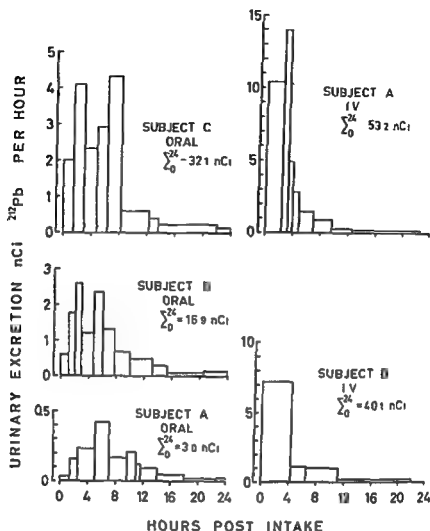


Fig 1 ^{212}Pb urinary excretion rate as a function of time for oral and intravenous intake

Twenty milliliters blood samples were taken from the antecubital vein using heparin as anticoagulant, and sampling at the times noted in the report of the results. The blood was centrifuged within 3 min after collection and the plasma was separated from the cells. Each fraction was weighed and counted for gamma radioactivity. A 5 cm diameter, 5 cm thick NaI(Tl) crystal was used as detector and two measurements were taken for each sample using single channel analyzer settings such that the ^{212}Pb and ^{212}Bi activity could be estimated separately. The blood fractions were next digested with conc. HNO_3 and hydrogen peroxide. The ^{212}Pb without addition of carrier was separated by use of the dithizone method (GIBSON). The 10 ml weak nitric acid solution containing

Table 1

Absorption of orally administered ^{212}Pb calculated by comparing the urinary excretion with that after intravenous administration

Subject	Age yr	Wgt kg	Dose μCi	Mode	Urinary loss* $\mu\text{Ci}/24$ hours	Absorption	
						μCi	% dose
A	59	75	1.08	iv	53.2	—	—
D	59	76	1.17	iv	40.1	—	—
A	59	75	5.05	oral	2.98	0.067	1.3
B	40	84	5.01	oral	16.9	0.404	8.1
C	27	63	4.80	oral	32.1	0.768	16.0

* iv decay corrected to midpoint of collection interval

the separated ^{212}Pb was evaporated on a 5 cm diameter stainless steel planchet yielding an essentially weight free deposit. After a lapse of 6 hours or more to permit ^{212}Pb — ^{212}Bi equilibrium to occur the planchet was counted for alpha activity in close proximity to a zinc sulfide layer phototube detector. The overall counting efficiency was 34 per cent as determined by comparison with a RaD + E standard. Chemical recovery was estimated by performing 10 analyses in which known amounts of ^{212}Pb were added to red cell and plasma samples from non-radioactive donors. The results indicated an average recovery of 90 per cent with a standard deviation of ± 7 per cent. This correction was applied to the experimental data.

Whole body counting. At intervals the subjects were counted in the low back ground laboratory (LINDALL & MAGI) at this institute. The procedure included scanning measurements and a series of localization studies. For both purposes the subject lay in a supine position. The arrangement for scanning used three 12.7×10.2 cm NaI(Tl) crystals placed equidistant on a collar surrounding the subject with each crystal face 40 cm from the subject's longitudinal axis. During measurement the collar has a reciprocating motion as well as a movement parallel to the subject axis. Details are available in the Whole Body Counter Directory of IAEA. For localization studies a single crystal looked through a 5 cm wide aperture formed by two 1 cm thick lead plates. The counting rate of a point source (^{212}Pb) moved along the longitudinal axis of the subject position decreased by half when removed in either direction from a point directly under the crystal center to a point 10 cm distant. In the experimental procedure each position was counted from the dorsal and the ventral aspect of the subject. The

counts obtained were stored in a 400 channel spectrum analyzer, read out, and converted to activity according to techniques in general use.

Conversion to absolute activity units The basis for estimating absolute activity depended on direct or indirect alpha counting rate comparison with a US Bureau of Standards RAD + F standard. Secondary standards prepared by passing thoron through 0.5 N HNO₃ solutions were calibrated by evaporating aliquots on stainless steel planchets and by counting rate comparisons with the standard. The standardized solutions were useful for evaluating, by gamma counting rate comparison, the activity of substances such as beer and urine which leave residues when evaporated and were therefore not suitable for direct alpha counting.

Results

²¹⁰Pb in feces and urine In the original planning of this research it was hoped that the personal habits of the subjects would conform to the ICRP gastrointestinal model and that the oral dose would be completely cleaned from the gut by 31 hours as specified. In sober fact, by 31 hours after intake, subjects A, B, and C had cleared 23, 0 and 17 per cent of the oral dose, by 48 hours 82, 69, and 77 per cent, by 72 hours 82, 69, and 77 per cent, and by 96 hours 99, 69 and 77 per cent. The above data are based on fecal sample measurements, with the measured activity decay adjusted to time of oral intake. The intervals without increase are periods in which no fecal samples were voided. As this pattern of excretion became apparent in the first oral experiment, it became evident that gastrointestinal absorption of ²¹⁰Pb could not uniformly be determined by whole body counting techniques. For example, if 10 per cent of a 5 μ Ci oral dose were absorbed, and if complete gut clearance required 96 hours, the absorbed ²¹⁰Pb would have decayed to 0.95 nCi, an activity below the threshold for measurement by this method. Accordingly, other methods were sought. The use of fecal measurements alone for a direct assessment of the unabsorbed ²¹⁰Pb was unsatisfactorily imprecise because of the large decay correction factor for low activity samples excreted at late times. Determination of absorption on the basis of the amount excreted in the urine in the first 24 hours was the method chosen. Accordingly, as stated above, the oral experiments were supplemented by two experiments in which ²¹⁰Pb was injected intravenously in order to define the per cent of the systemic burden which would appear in the urine.

The results of the measurements of urine samples from all five experiments appear in Fig. 1. Each sample was decay adjusted from the time of measurement to the mid point of the collection period. The cumulative excretion from

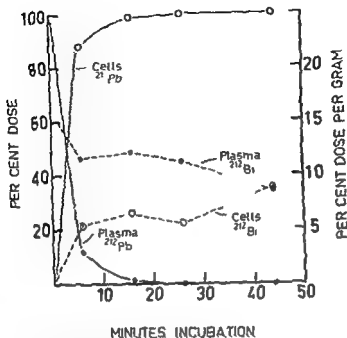


Fig 2 In vitro uptake of ^{210}Pb and ^{210}Bi by the blood cells. The solid lines pertain to the left ordinate scale and the dotted lines to the right ordinate scale.

0 to 24 hours was noted for each experiment. By reference to the injected doses listed in Table 1 it may be calculated that when ^{210}Pb was administered intravenously 4.9 per cent (subject A) and 3.4 per cent (subject B) of the dose appeared in the 24 hour urine collection. The average value 4.15 per cent was used to estimate absorption in the oral experiments yielding the results entered in Table 1.

After intravenous injection subject A excreted 0.29 per cent dose in the fecal collection period 0 to 48 hours. Subject D excreted 0.25 per cent dose for the same fecal collection period. These estimates are maximized since all sample measurements were decay adjusted to injection time.

^{210}Pb uptake by blood cells. As an adjunct to the main experiments a preliminary in vitro experiment was performed in which 10 ml volumes of heparinized blood were incubated with added ^{210}Pb + ^{210}Bi at 37°C in a water bath. At pre-selected times the blood samples were removed and centrifuged. The plasma and cell fractions were then assayed for ^{210}Pb and ^{210}Bi activity by gamma

Table 2

^{210}Pb and ^{210}Bi content of plasma and blood cells in per cent absorbed or injected dose per gram referred to sampling time except as otherwise indicated

Subject and mode	Sample	Hours post dose	Plasma	Cells	Cells	Cells	Cells	Total cells
			$^{210}\text{Pb}^*$	$^{210}\text{Pb}^*$	$^{210}\text{Pb}^{**}$	$^{210}\text{Bi}^{**}$	$t = 0$	$t = 0$ dose
A intravenous	1	0.33	0.00036	0.0106	0.0104	—	0.0107	37
	2	1.67	0.00009	0.0124	0.0140	—	0.0147	44
	3	1.05	—	—	0.0150	—	0.0195	59
	4	6.75	—	0.0124	0.0113	—	0.0184	56
	5	49.75	—	0.00054	—	—	0.0139	47
B oral	1	2.50	0.00009	0.0073	0.0057	0.0033	0.0077	76
	2	6.00	0.00009	0.0130	0.0116	0.0115	0.0182	62
	3	8.00	0.00006	0.0136	0.0147	0.0111	0.0734	79
	4	24.50	0.00006	0.0058	0.0031	0.0079	0.0221	75
C oral	1	2.60	0.00025	0.0086	0.0076	0.0052	0.0096	24
	2	6.10	0.00008	0.0124	0.0123	0.0096	0.0184	47
	3	8.00	0.00011	0.0132	0.0124	0.0117	0.0216	55
	4	24.50	—	0.0048	0.0055	0.0031	0.0255	65
	5	48.50	—	0.0010	0.0010	0.0012	0.0236	10
D intravenous	1	0.35	0.00033	0.0221	—	—	0.0226	19
	2	1.58	0.00011	0.0250	0.0260	0.0210	0.0785	89
	3	7.10	0.000052	0.0190	0.0700	0.0190	0.0310	91
	4	23.63	—	0.0059	0.0061	0.0060	0.0280	86
	5	47.57	—	0.0012	0.0016	—	0.0375	100

* Measured by alpha counting

** Measured by gamma counting

measurement as described above. The results are shown in Fig. 2. It is seen that at 16 min the cells have taken up 99 per cent of the ^{210}Pb added to the whole blood. The uptake of ^{210}Bi by the cells occurred at a slower rate and gives no evidence of a tendency to concentrate with respect to the plasma.

In view of these tendencies it is not surprising that the results after oral or intravenous administration as shown in Table 2 demonstrate only small amounts of ^{210}Pb in the plasma fraction of the drawn blood samples. The estimation of ^{210}Pb in the cells shows satisfactory agreement between the two measurement methods. The first column of the table lists results obtained by assuming that the total mass of circulating blood cells in grams is equal to 40.3 times the body weight in kg (BEST & TAYLOR). Since the ^{210}Pb content per gram cell (is shown

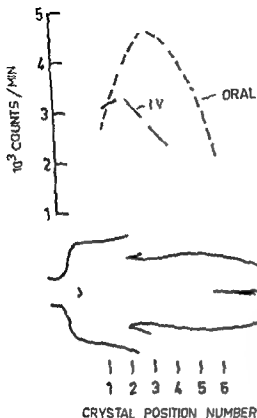


Fig. 3 Comparison of radioactivity profile after intravenous (+ 6 hours) and oral (+ 98 hours) intake for subject A. Actual counting rate was decay adjusted to time of intake and for oral results normalized to 1 μCi intake.

in the next to last column) has been decay corrected to time of intake it may be seen that little if any ^{21}Pb is lost except by decay. The data for all subjects show an increase in cell content (last two columns) for the early sampling times believed to be due to the return of ^{21}Pb from the tissues to the blood as the plasma concentration is decreased leading to further uptake by the cell. The generally higher estimates of ^{21}Pb uptake in the total cells for subject D are obviously in error and it seems likely that the formula used to calculate the total cell mass resulted in an overestimate in this case. It is recognized (GLASSER) that such formulae may be in error when applied to specific normal individuals.

Comparison of ^{210}Bi and ^{210}Pb metabolism. Although the data on the fate of ^{210}Bi are less complete than are the data for ^{210}Pb it has been found that at the time of voiding the bismuth activity in the urine samples is about twice that of

Table 2

²¹⁰Pb and ²¹⁰Bi content of plasma and blood cells in per cent absorbed or injected dose per gram referred to sampling time except as otherwise indicated

Subject and mode	Sample	Hours post dose	Plasma	Cells	Cells	Cells	Cells	Total cells
			²¹⁰ Pb*	²¹⁰ Pb*	²¹⁰ Pb**	²¹⁰ Bi**	²¹⁰ Pb t = 0	²¹⁰ Pb t = 0 dose
A intravenous	1	0 33	0 00036	0 0106	0 0104	—	0 0107	32
	2	1 67	0 00009	0 0124	0 0140	—	0 0147	44
	3	4 05	—	—	0 0150	—	0 0195	59
	4	6 75	—	0 0124	0 0113	—	0 0184	56
	5	49 75	—	0 00054	—	—	0 0139	49
B oral	1	2 50	0 00009	0 0073	0 0057	0 0033	0 0077	26
	2	6 00	0 00009	0 0130	0 0116	0 0115	0 0182	69
	3	8 00	0 00006	0 0136	0 0142	0 0111	0 0234	79
	4	24 50	0 00006	0 0058	0 0031	0 0079	0 0221	75
C oral	1	2 60	0 00075	0 0086	0 0076	0 0052	0 0096	74
	2	6 10	0 00008	0 0124	0 0123	0 0096	0 0184	47
	3	8 00	0 00011	0 0132	0 0124	0 0117	0 0216	55
	4	24 50	—	0 0048	0 0055	0 0031	0 0255	65
	5	18 50	—	0 0010	0 0010	0 0012	0 0236	60
D intravenous	1	0 35	0 00033	0 0221	—	—	0 0226	69
	2	1 58	0 00011	0 0250	0 0260	0 0210	0 0285	89
	3	7 10	0 000052	0 0190	0 0200	0 0190	0 0310	93
	4	23 63	—	0 0059	0 0061	0 0060	0 0280	86
	5	47 57	—	0 0012	0 0016	—	0 0375	100

* Measured by alpha counting

** Measured by gamma counting

measurement as described above. The results are shown in Fig. 2. It is seen that at 16 min the cells have taken up 99 per cent of the ²¹⁰Pb added to the whole blood. The uptake of ²¹⁰Bi by the cells occurred at a slower rate and gives no evidence of a tendency to concentrate with respect to the plasma.

In view of these tendencies, it is not surprising that the results after oral or intravenous administration as shown in Table 2 demonstrate only small amounts of ²¹⁰Pb in the plasma fraction of the drawn blood samples. The estimation of ²¹⁰Pb in the cells shows satisfactory agreement between the two measurement methods. The last column of the table lists results obtained by assuming that the total mass of circulating blood cells in grams is equal to 40.3 times the body weight in kg (BRIST & TAYLOR). Since the ²¹⁰Pb content per gram cell (as shown

Table 2 When the absolute concentrations of ^{21}Pb in the blood of subjects B and C are converted into per cent absorbed dose the resulting values are quite comparable to those obtained in the two intravenous experiments This would not be expected if the calculated systemic burdens of subjects B and C were greatly in error

Proceeding on the grounds that the wide range in fraction absorbed is real it is pertinent to inquire as to the possible causes of variation The three subjects in the oral experiment were healthy active individuals Compared with the ICRP (1959) reference man who has 2 grams potassium per kg bodyweight subjects A, B and C had 1.93, 1.89 and 2.63 grams per kg These values suggest normal and above average ratios of lean body mass to total weight The only suggestive relationship is the decrease in absorption of ^{21}Pb with increase in subject age The present data are insufficient to prove age dependence and may represent fortuitous sampling of extremes on a curve of normal biologic variability Further interpretation makes it likely that there is a group of individuals for which the absorption value of 8 per cent is not conservative for health protection uses Further experiments are needed to define the size of this group

Concentration of ^{210}Pb in the blood cells The concentration of lead in the blood cells was observed by early workers (DAVIE 1907; BEHRENS et al. 1927) and confirmed many times since HEVEY & NILLIN (1953) reported that 6 hours after intravenous injection of ^{21}Pb into man 45 per cent of the injected amount was in the blood cells STOVER (1959) found for dogs, that 65 per cent of an intravenous dose of ^{21}Pb was in the blood cells at 5 hours SCHUBERT & WHITE (1952) injected carrier free ^{210}Pb into rats and detected 17 per cent of the dose in the blood cells at 30 minutes The rate of loss from the red cells (not including radioactive decay) was 0.0187 per hour for dogs (STOVER) and 0.0231 per hour for rats (SCHUBERT & WHITE) HEVEY & NILLIN stated that in man the loss rate is less than 0.04 per hour

The data in Table 2 show no constant loss rate and render unlikely a loss rate greater than 0.007 per hour If it be assumed for man that the death of the red cell releases the fixed lead and that the lead is removed from the body for example by secretion in the bile a minimum release rate can be calculated Since the average life span of the human red cell is 120 days the equivalent lead loss rate would be 0.0083 per day or 0.00035 per hour Neither the data of HEVEY & NILLIN nor our findings can be regarded as excluding this interpretation On the positive side a test of its feasibility can be applied by using data from the classical lead studies of KENDRICK (1943) He found that the daily food intake of stable lead by occupationally unexposed individuals is about 0.35 mg and that the corresponding level in the blood is 0.030 mg per 100 ml If the blood volume

the lead. The blood cells in general show (Table 2) slightly less ^{210}Bi than ^{210}Pb , leading to the interpretation that the rate of ^{210}Bi loss from the cells must be low in respect to its rate of formation from ^{210}Pb . HARRIS (1952) with ThX injected into rabbits, found an excess of ^{210}Bi over ^{210}Pb in the urine and the reverse to be true for the blood cells. STOVER (1959), after intravenous injection of ^{210}Pb into dogs, found an excess of ^{210}Bi over ^{210}Pb in the urine, and no disequilibrium for blood cells measured 20 min after sampling. Finally, the whole body counter localization studies in the present experiments showed no marked differences in the overall body distribution of ^{210}Pb and ^{210}Bi .

Whole body counter findings Scanning measurements made with the whole body counter facility in the two intravenous experiments showed the expected 10.6 hour half life decrease when small corrections were made for urinary loss. For the three oral experiments the activity found at the latest scan (about 48 hours), decay corrected to $t=0$, yielded values of 18, 39, and 23 per cent of the ingested dose for subjects A, B, and C. As explained above, these amounts include activity in the lower bowel which was voided subsequently. With the exception of subject A, who voided 17 ± 1 per cent at 73 hours, the delay in voiding resulted in activities near the threshold of detection, subject to large correction factors for decay and not of use in the estimation of the absorbed fraction.

The measurements with the lead columnated crystal yielded results of which the data from examination of subject A presented in Fig. 3 is a typical example. The oral experiment data, measured 28 hours after intake and normalized to time of intake and to $1 \mu\text{Ci}$ dose, shows an activity peak in the lower bowel region. The survey 6 hours after intravenous injection (counts corrected to injection time) shows a concentration of activity in the blood rich areas of the heart, lungs, and liver. This result agrees well with what might be expected from the high ^{210}Pb content of the blood cells.

Discussion

Absorption of ^{210}Pb The wide variation between the absorption of subject A and subject C (12 times) calls for comment. The validity of the indirect method used to calculate absorption depends on the assumptions (1) that the fraction of the systemic ^{210}Pb excreted in the urine will be the same whether entry is via the gut or by intravenous injection and (2) that this fraction does not vary greatly from one healthy individual to another. Both these assumptions are biologically plausible but proof that they apply to excretion of lead by man is lacking.

Support for the calculated absorption values comes from the blood data in

Table 2 When the absolute concentrations of ^1Pb in the blood of subjects B and C are converted into per cent absorbed dose the resulting values are quite comparable to those obtained in the two intravenous experiments. This would not be expected if the calculated systemic burdens of subjects B and C were greatly in error.

Proceeding on the grounds that the wide range in fraction absorbed is real it is pertinent to inquire as to the possible causes of variation. The three subjects in the oral experiment were healthy active individuals. Compared with the ICRP (1959) reference man, who has 2 grams potassium per kg bodyweight, subjects A, B and C had 1.93, 1.89 and 2.63 grams per kg. These values suggest normal and above average ratios of lean body mass to total weight. The only suggestive relationship is the decrease in absorption of ^1Pb with increase in subject age. The present data are insufficient to prove age dependence and may represent fortuitous sampling of extremes on a curve of normal biologic variability. Either interpretation makes it likely that there is a group of individuals for which the absorption value of 8 per cent is not conservative for health protection uses. Further experiments are needed to define the size of this group.

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of an adult is taken as 5 400 ml (ICRP), the total lead burden carried by the blood becomes 1.62 mg. Assuming an average absorption of 11 per cent from the gastrointestinal tract, and that 50 per cent of the absorbed lead is fixed by the blood cells, the daily uptake of lead becomes 0.014 mg. Since the lead concentration in the blood cells must be in a steady state the loss rate constant is 0.014 divided by 1.62 = 0.0086 per day, a value very near to the rate of 0.0083 per day based on the proposal that lead is lost only by death of the blood cell.

If this interpretation is valid it enables a circumstantial statement of the protection against lead poisoning given by the lead fixing property of the red blood cell. The maximum lead binding capacity of the cells can be estimated from the report by KENNEDY *et al.* (1943). They performed experiments in which two human subjects were given supplementary soluble lead by mouth at the rate of 1 and 2 mg per day over periods of years. From examination of their data it is found that the blood level rises to a mean value of about 0.06 mg lead per 100 ml and does not greatly exceed this. If this concentration represents saturation the blood cell mechanism could turn over about 0.028 mg lead per day with only transient increases in the plasma concentration. Since by hypothesis the cells are able to pick up only half of the lead introduced from the gut, this would conform to a total systemic intake of about 0.056 mg per day. If the systemic intake exceeds this rate, the average plasma lead concentration must rise. This leads to proportionally increased skeletal deposition and urinary excretion. Toxicity symptoms might be anticipated at plasma lead concentrations up to 4 to 5 times above the unexposed mean levels, on the grounds that equivalent increases in urinary excretion rates have been observed (KENNEDY) to be associated with lead intoxication.

Comparison of behavior of carrier free ^{212}Pb and stable lead In terms of the discussion above, it is apparent that the ^{212}Pb in oral and intravenous administration was no longer carrier free after it entered the gut or the circulatory system. Accordingly, absorption from the gut should not differentiate between ^{212}Pb and stable ions as such. If ^{212}Pb is introduced with supplementary lead in amounts so large as to saturate the binding sites of the blood cells, marked differences in tissue distribution and urinary excretion might be expected.

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SUMMARY

The gastrointestinal absorption on administration of ^{210}Pb by mouth to three human subjects was found to be respectively 13.8% and 16.0%. The absorption was determined by a comparison of the 24 hour urinary excretion of these subjects with the average excretion in the same period by two subjects who received ^{210}Pb intravenously. The only obvious factor related to the wide range of absorption was that of age, increasing age being associated with decreasing absorption. The average value of 8% is equal to that used by ICRP. It is pointed out that this choice may not be conservative for an appreciable fraction of the population. The ^{210}Pb concentrations in the blood cells as a function of time after oral or intravenous administration suggest that lead may be released from the binding sites only when the red cells die. The relationship of this proposal to permissible intakes of stable lead is considered.

ZUSAMMENFASSUNG

Bei oraler Verabreichung von ^{210}Pb in drei Personen wurden gastrointestinale Absorptionswerte von 13,8% und 16% erhalten. Zur Bestimmung der Absorption wurde die 24 Stunden Urinausscheidung dieser Personen mit der durchschnittlichen Ausscheidung während derselben Periode in zwei Personen verglichen, bei denen ^{210}Pb intravenös verabreicht wurde. Der einzige Faktor, der in positiver Korrelation zu dem weiten Absorptionsbereich stand, war das Alter: mit zunehmenden Lebensalter nimmt die Ausscheidung ab. Der Durchschnittswert von 8% ist derselbe wie der von ICRP angegebene; dieser sollte aber nicht als ausschlaggebend für einen beträchtlichen Anteil der Bevölkerung betrachtet werden. Die Konzentrationen von ^{210}Pb in den Blutzellen im Verhältnis zur Zeit nach der oralen oder intravenösen Verabreichung deuten darauf hin, dass stabiles Blei von den Retentionsstellen nur dann freigesetzt wird, wenn die rote Blutzelle stirbt. Diese Frage wird hinsichtlich der zulässigen Aufnahme von stabilem Blei im Organismus diskutiert.

RÉSUMÉ

Après administration de ^{210}Pb par voie orale à trois sujets humains, on a constaté des taux d'absorption gastro-intestinale de 13,8% et 16%. La méthode de détermination de l'absorption a été de comparer l'excrétion urinaire de 24 heures de ces sujets avec l'excrétion moyenne au cours de la même période de deux sujets à qui ^{210}Pb avait été administré par voie intraveineuse. Le seul facteur nettement en rapport avec ces taux d'absorption très différents est l'âge: l'absorption diminuant quand l'âge augmente. La valeur moyenne de 8% est celle qui est donnée par l'ICRP. Les auteurs soulignent que ce choix ne peut pas convenir pour une partie appréciable de la population. L'étude des concentrations de ^{210}Pb dans les cellules sanguines en fonction du temps après administration orale ou intraveineuse fait penser que le plomb ne peut être libéré que quand le globule rouge meurt. Les auteurs examinent les conséquences de cette hypothèse sur la quantité admissible de plomb stable introduit dans le corps.

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Comparison of behavior of 'carrier free' ^{210}Pb and stable lead. In terms of the discussion above, it is apparent that the ^{210}Pb in oral and intravenous administration was no longer carrier free after it entered the gut or the circulatory system. Accordingly, absorption from the gut should not differentiate between ^{210}Pb and stable ions as such. If ^{210}Pb is introduced with supplementary lead in amounts so large as to saturate the binding sites of the blood cells, marked differences in tissue distribution and urinary excretion might be expected.

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AUTORADIOGRAPHIC STUDIES ON DISTRIBUTION OF RADIOCOBALT CHLORIDE IN PREGNANT MICE

by

HANS FLODIN

Cobalt is present in small amounts in all animal material. As yet no essential physiological function of cobalt is known except its presence in the vitamin B₁₂ molecule.

Deficiency symptoms are not known in other animals than sheep and cattle, which need cobalt for their microbiologic synthesis of vitamin B₁₂. In large doses cobalt acts upon blood forming organs causing the formation of renal erythropoietin (FISHER et coll 1962) and producing polycythemia (WALTNER & WALTNER 1929 MARSHALL 1935) and hyperglycemia (VON HOLT & VON HOLT 1954 HULTQUIST 1959 BOYD & MACLEAN 1959). Several investigations concerning the metabolism of cobalt have been carried out in recent years using autoradiographic and scintillometric techniques (COMAR & DAVIS 1947 BRAUDE et coll 1949 ULRICH & COPP 1951 MELRMAN & ODEBLAD 1956 CARLBERGER 1961 CARLBERGER et coll 1961 KASANEV et coll 1964). The body distribution of cobalt has been studied in various species e.g. the rat (CUTHBERTSON et coll 1950 ULRICH & COPP 1951 MELRMAN & ODEBLAD 1956 KASANEV et coll 1964) rabbit (COMAR & DAVIS 1947 VOLA et coll 1953) dog (LEE & WOL

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REFERENCES

- BEHRENS B and PACHUR R Die Verteilung und der Zustand kleinster Bleimengen im Blut
Arch exp Path Pharmac 122 (1927), 319
- BEST C H and TAYLOR N B The physiological basis of medical practice 5th edition pp
18—19 Williams and Wilkins Co Baltimore 1950
- DAUWE O Contribution à l'étude expérimentale du saturnisme aigu Arch inter Pharma
codyn 17 (1907) 387
- DIRECTORY OF WHOLE BODY MONITORS To be published by IAEA Vienna
- GIBSON W M The radiochemistry of lead NAS NS 3040
- GLASSER O Medical physics Vol 1, p 123 Year Book Publishers Inc Chicago 1944
- HARDERS E Untersuchungen über Verteilung und Ausscheidung der in vivo entstehenden
Folgeprodukte des Thorium X Naturforschung 7 B (1952) 363
- HEVESY G and NYLIN G Application of thorium B labelled red corpuscles in blood volume
studies Circulation Res 1 (1953) 102
- HURSH J H and LOVAAS A Preparation of a dry Th 228 source of thoron J inorg nucl
Chem 29 (1967) 599
- IAEA See Directory of whole body monitors
- ICRP Recommendations See Permissible dose for internal radiation
- KFIIOF R A Exposure to lead Occup Med 3 (1943) 156
- CHIOIAK J HUBBARD D M et coll Experimental studies on lead absorption and excretion
and their relation to the diagnosis and treatment of lead poisoning J industr Hyg 25
(1943) 71
- LINDFLL B and MAGI A A new laboratory for whole body counting p 135—137 Acta radiol
(1966) Suppl No 254
- PERMISSIBLE DOSE FOR INTERNAL RADIATION Recommendations of the International Commission
on Radiological Protection Report of Committee II ICRP Publication 2 Pergamon Press
New York 1960
- SCHUBERT J and WHITE M R Effect of sodium and zirconium citrates on distribution
and excretion of injected radiolead J Lab clin Med 39 (1952) 260
- STOVER B J Pb²¹⁰ (ThB) tracer studies in adult beagle dogs Proc Soc exp Biol 100
(1959) 269

Plexus choroideus Heart blood Pancreas Intestines Fetus



Fig 2 Autoradiogram of $^{60}\text{CoCl}$ in a pregnant mouse 4 hours after intra-venous injection. The distribution pattern is similar to that after one hour. In addition to the liver and pancreas, there is high concentration in plexus choroideus and costal cartilages.

cartilages and fetal skeleton accumulated cobalt to a large extent especially from one day and onwards (Figs 3 and 4). The radioactivity in the fetuses noticeable as early as one hour after the injection (Fig 1) was during the first days selectively localized to the fetal bones. The distribution in different tissue groups at different intervals will be described below.

Blood As early as one hour after injection the concentration of radiocobalt in the blood was low. Compared to the liver it was about 8 times lower, but it was at the same level as in the lungs, placenta and salivary glands. The activity then gradually disappeared from the blood, a process which was largely completed after 24 hours.

Cartilage One hour after injection the nasal and costal cartilages of the mother showed high concentration of cobalt. By this time radioactivity was also observable in fetal bone. The concentration of radiocobalt in cartilage increased with time, and 4 days after injection it was about 4 times higher than in the liver (Fig 4). From 24 hours after the injection and onwards the cartilages in trachea and larynx of the mother had the highest concentration (Fig 3).

Digestive organs The liver had high concentration of radiocobalt at all times studied. In the pancreas the initial accumulation was at the same level as in the liver, the activity then slightly decreased, but after 24 hours it was still among the highest in the body. One hour after injection the salivary glands had about

Salivary glands Mammary glands Liver Kidney Placentae Fetus



Fig 1 Autoradiogram of $^{60}\text{CoCl}_2$ in a pregnant mouse one hour after intravenous injection. The liver, pancreas, kidneys and mammary glands have the highest concentration. Radioactivity already observable in the fetuses is mainly localized to fetal bone.

TERINK 1955), sheep (ROTHERT et coll 1953) and cattle (COMAR & DAVIS 1947). In this investigation the distribution in pregnant mice of radiocobalt, $^{60}\text{CoCl}_2$, has been studied using whole body autoradiography.

Methods. Pregnant NMRI mice were intravenously injected with water solutions of $^{60}\text{CoCl}_2$ obtained from The Radiochemical Centre, Amersham, England. An amount of 0.2 ml, corresponding to a total activity of $10 \mu\text{Ci}$, was given to each mouse. At different times after injection the animals were anaesthetized and immersed into a mixture of solid carbon dioxide and hexane (-78°C). The times between injection and sacrifice were 1 hour, 4 hours, 24 hours, 4 days and 16 days. The autoradiographic method has been described by ULLBERG (1954, 1958).

Sagittal 20μ sections through the whole frozen animals were cut at different levels and dried at -10°C . The films used were Structurix (Gevaert) and Kodirex (Kodak), and the exposure time varied between 2 weeks and 3 months.

An isotope staircase, representing known amounts of ^{60}Co in twofold serial dilutions was placed together with the section on some of the films. The amount of activity in various tissues could then be compared by densitometry.

Results

The highest concentration of radiocobalt in the body was observed in the cartilaginous structures, liver, kidneys and pancreas. High activity in urinary ways and intestinal contents indicated renal and fecal excretion. Maternal

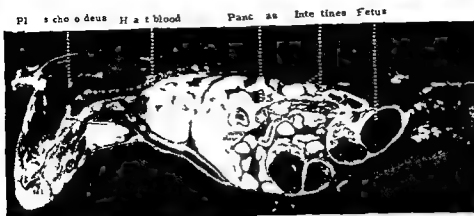


Fig 2 Autoradiogram of $^{60}\text{CoCl}$ in a pregnant mouse 4 hours after intravenous injection. The distribution pattern is similar to that after one hour. In addition to the liver and pancreas there is high concentration in plexus choroideus and costal cartilages.

cartilages and fetal skeleton accumulated cobalt to a large extent especially from one day and onwards (Figs 3 and 4). The radioactivity in the fetuses noticeable as early as one hour after the injection (Fig 1) was during the first days selectively localized to the fetal bones. The distribution in different tissue groups at different intervals will be described below.

Blood As early as one hour after injection the concentration of radiocobalt in the blood was low. Compared to the liver it was about 8 times lower but it was at the same level as in the lungs, placenta and salivary glands. The activity then gradually disappeared from the blood, a process which was largely completed after 24 hours.

Cartilage One hour after injection the nasal and costal cartilages of the mother showed high concentration of cobalt. By this time radioactivity was also observable in fetal bone. The concentration of radiocobalt in cartilage increased with time and 4 days after injection it was about 4 times higher than in the liver (Fig 4). From 24 hours after the injection and onwards the cartilages in trachea and larynx of the mother had the highest concentration (Fig 3).

Digestive organs The liver had high concentration of radiocobalt at all times studied. In the pancreas the initial accumulation was at the same level as in the liver, the activity then slightly decreased but after 24 hours it was still among the highest in the body. One hour after injection the salivary glands had about

Salivary glands Mammary glands Liver Kidney Placentae Fetus



Fig. 1. Autoradiogram of $^{60}\text{CoCl}_2$ in a pregnant mouse one hour after intravenous injection. The liver, pancreas, kidneys and mammary glands have the highest concentration. Radioactivity already observable in the fetuses is mainly localized to fetal bone.

TERINK 1955), sheep (ROTHERY et coll. 1953) and cattle (COMAR & DAVIS 1947). In this investigation the distribution in pregnant mice of radiocobalt, $^{60}\text{CoCl}_2$, has been studied using whole body autoradiography.

Methods. Pregnant NMRI mice were intravenously injected with water solutions of $^{60}\text{CoCl}_2$ obtained from The Radiochemical Centre, Amersham, England. An amount of 0.2 ml, corresponding to a total activity of 10 μCi , was given to each mouse. At different times after injection the animals were anaesthetized and immersed into a mixture of solid carbon dioxide and hexane (-78°C). The times between injection and sacrifice were 1 hour, 4 hours, 24 hours, 4 days and 16 days. The autoradiographic method has been described by ULIBRÉ (1954, 1958).

Sagittal 20 μ sections through the whole frozen animals were cut at different levels and dried at -10°C . The films used were Structurix (Gevaert) and Kodirex (Kodak), and the exposure time varied between 2 weeks and 3 months.

An isotope staircase, representing known amounts of ^{60}Co in twofold serial dilutions, was placed together with the section on some of the films. The amount of activity in various tissues could then be compared by densitometry.

Results

The highest concentration of radiocobalt in the body was observed in the cartilaginous structures, liver, kidneys and pancreas. High activity in urinary ways and intestinal contents indicated renal and fecal excretion. Maternal

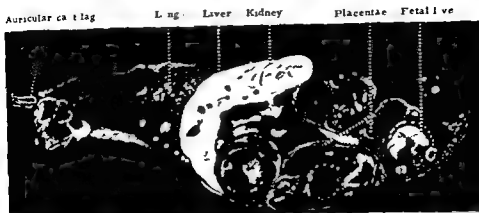


Fig 4 Autoradiogram of $^{60}\text{CoCl}$ in a pregnant mouse 4 days after intravenous injection. Cartilages and fetal bone have the highest concentration. Some accumulation may also be seen in the fetal liver.

pituitary and thyroid During the first days after injection the adrenal cortex showed higher concentration than the adrenal medulla. However, there was a gradual increase in the adrenal medulla which 16 days after the injection had passed the cortex and showed a fairly high concentration (Fig 5).

Central nervous system The uptake of ^{60}Co in the central nervous system was very low throughout the study. The choroid plexus however had a high accumulation of cobalt as early as after one hour. Four hours after injection it was almost as high as in the liver (Fig 2).

Mammary glands The accumulation of radiocobalt in the mammary glands was high. After 24 hours it was at the same level as in the liver and kidneys.

Fetus The total fetal accumulation of ^{60}Co at all the intervals studied was lower than that of the dam. Some fetal uptake was observable as early as one hour after injection. A selective accumulation as high as in the maternal cartilages was seen in the fetal skeleton during the first days after administration. There was low concentration in the soft tissues of the fetuses except the liver which showed a fairly high concentration 4 days after injection. After 16 days the fetuses had no longer any noticeable radioactivity.

Placenta The placenta showed a moderate accumulation of radiocobalt throughout the study with a slight increase during the first 24 hours. The radioactivity in the yolk sac epithelium was higher.

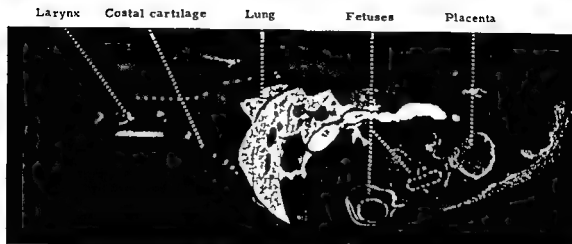


Fig 3 Autoradiogram of $^{60}\text{CoCl}_2$ in a pregnant mouse 24 hours after intravenous injection. The concentration is very high in maternal cartilages and fetal bone.

the same concentration as the blood, placentae and lungs, there were differences between the salivary glands: the sublingual salivary gland accumulated more radio-cobalt than the submaxillary and parotid salivary glands, with a maximum after 4 days (Fig 4). The activity in the gastric mucosa and contents was fairly low, but in the intestinal mucosa and contents there was high activity during the first 24 hours after injection. The concentration in the gall bladder did not exceed the blood level.

Respiratory organs In addition to the cartilaginous structures cobalt was also to a large extent taken up by the mucous secretion in the respiratory tract. In the lungs the accumulation was higher in the bronchioli than in the surrounding lung tissue. The maximum uptake was seen 24 hours after the injection (Fig 3).

Kidneys The accumulation of cobalt was high in the kidneys with a peak in concentration during the first 4 hours. The radioactivity was mainly localized to the inner parts of the cortex (Fig 1). After 4 days the activity was still as high as in the liver.

Myocardium The concentration in the myocardium was fairly low with a relative increase after several days. Sixteen days after administration the radioactivity in the myocardium was about twice that of the liver (Fig 5).

Endocrine organs The endocrine organs showed fairly low concentrations of radiocobalt. The accumulation was a little higher in the adrenals than in the

of cobalt e.g. mammary glands, salivary glands (mainly the mucous sublingual salivary glands), lingual and palatine mucous glands, mucous secretion in the respiratory ways and mucous and serous membranes in the gastro-intestinal tract. In this respect the distribution of cobalt is similar to that of sulphate which to a large extent accumulated in cartilages and mucous glands (ULLBERG, unpublished).

The distribution pattern of cobalt was entirely different compared to the pattern obtained in similar autoradiographic investigations with $^{60}\text{CoB}_2$ (ULLBERG et coll. 1967). This proved however, which was expected, that vitamin B_{12} is not metabolized to inorganic cobalt in the body.

Acknowledgement

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SUMMARY

The distribution of $^{60}\text{CoCl}$ in pregnant mice has been studied by whole body autoradiography. The highest accumulation of radiocobalt occurred in the maternal cartilages, fetal skeleton, liver, kidneys and pancreas. Within the fetus the concentration was almost selectively localized to the bone. The mammary glands, salivary glands, placenta, yolk sacs, lungs and intestinal walls and contents also accumulated the isotope, though in smaller degree. The high concentration in cartilaginous structures is discussed.

ZUSAMMENFASSUNG

Die Verteilung des Radiokobalt Chlorides wurde mittels Ganzkörper Autoradiographie an trächtigen Mäusen studiert. Bevorzugt wurde Radiokobalt in der mütterlichen Knorpeln, im fetalen Skelet, in der Leber, den Nieren und dem Pankreas abgelagert. Im Fetus war die Aufspeicherung fast ausschließlich zu den Knochen konzentriert. Radiokobalt wurde auch in den Brust- und Speicheldrüsen, in der Plazenta, in den Dottersäcke, Lungen, Darmwände und in dem Darminhalt auf gespeichert, aber nur in geringerem Masse. Die hohe Aufnahme im Knorpel wird diskutiert.

RÉSUMÉ

La distribution du $^{60}\text{CoCl}$ chez les souris gravides a été étudiée par autoradiographie du corps entier. L'accumulation la plus forte de radio cobalt se trouve dans les cartilages de la mère et dans le squelette, le foie, les reins et le pancréas du fœtus. Dans le fœtus la concentration se localise presque électivement dans l'os. Les glandes mammaires, les glandes salivaires, les placentas, les sacs vitellins, les poumons et la paroi et le contenu de l'intestin fixent aussi l'isotope, à un moindre degré. L'auteur étudie la haute concentration de l'isotope dans les structures cartilagineuses.

Brain Costal cartilage Myocardium Stomach Adrenal medulla Intestines Fetuses



Fig 5 Autoradiogram of $^{60}\text{CoCl}_2$ in a pregnant mouse 16 days after intravenous injection. The concentration in the liver and kidneys has decreased. The accumulation is highest in the costal cartilages and the myocardium.

Discussion

The present investigation showed a high concentration of cobalt in cartilage as previously described (CARIBERGER 1961). In the adult animals the nasal costal, tracheal and articular cartilages, which are of the hyaline type, and the elastic laryngeal and auricular cartilages accumulated most of the injected radiocobalt chloride. The bones of the skull, the periosteum of the vertebrae and the pelvic bone also accumulated cobalt. In the fetuses where the radioactivity was almost selectively localized to the fetal skeleton, the uptake was highest in hyaline cartilage of the type that remains as cartilage in the adult animal. One exception was the fetal cranial bones which like the cranium of the dam, also showed a high accumulation of cobalt. These are the only bones in the body which are formed through intramembraneous ossification. The fairly rapid accumulation of cobalt in maternal cartilages and the fetal skeleton is surprising with regard to the absence of blood vessels in these tissues. Autoradiographic investigations of the distribution of Na (HUGGERT et coll 1961) and ^{137}Cs (NELSON et coll 1961) have also shown higher accumulation of these elements in cartilage than in other tissues. These authors suggested that cartilage may act as cation exchanger and that rapid accumulation in cartilage hardly can be due to incorporation into organic compound. Besides the uptake in cartilage there was very little similarity in the distribution between Cs, Na and Co.

Cartilage is composed of collagen and chondromucoid. There may exist a relationship between the presence of different glucoproteides and the uptake of cobalt since other organs containing these substances also show high accumulation.

EFFECT OF ANATOMICAL IRREGULARITIES ON THE DOSE IN ELECTRON BEAM THERAPY

by

E. KARJALAINEN, M. BRENNER and A. RYTILÄ

Although high energy electrons have been used in therapy for many years little still seems to be known regarding the effect of irregularities of human anatomy on the dose distribution. When such irregularities are due to bodies of limited width, then perturbations of the normal dose distribution, as seen in homogeneous tissue, may cause either small areas of overdose (hot spots) or areas of underdose (cold areas). The former may be large enough to damage vital organs or to develop necroses; the latter may allow tumour cells to survive treatment and thus lead to recurrence. These assumptions have constantly worried therapists and physicists. To calculate the effect of irregularities by theoretical means seems a tedious approach, the effect being dependent on the geometrical dimensions of the perturbing structures. The application of the Monte Carlo technique would be a time consuming task even for a single case. The present experimental approach is comparable to the investigations of BREITLING & VOGL (1963) and NETTELAND (1965) but has been accomplished in a way to facilitate the understanding of the effect of irregularities in clinical practice. A comparison with the corresponding changes in cobalt therapy has been made.

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REFERENCES

- BOYD G S and MACLEAN N Observations on the metabolic and histological effects of cobalt chloride in the rabbit, with particular reference to cobalt induced hypercholesterol aemia *Quart J exp Physiol* 44 (1959), 394
- BRAUDE R, FREE A A PAGE J E and SMITH E L The distribution of radioactive cobalt in pigs *Brit J Nutr* 3 (1949) 289
- CARLBERGER G Kinetics and distribution of radioactive cobalt administered to the mammalian body *Acta radiol* (1961) Suppl No 205
- MAGNUSSON G and MEURMAN L The uptake of cobalt in some endocrine organs *Acta med scand* 170 (1961) No 4
- COMAR C L and DAVIS G K Cobalt metabolism studies III Excretion and tissue distribution of radioactive cobalt administered to cattle *Arch Biochem* 12 (1947) 257
- Cobalt metabolism studies IV Tissue distribution of radioactive cobalt administered to rabbits swine and young calves *J Biol Chem* 170 (1947) 379
- CUTHBERTSON W F J FREE A A and THORNTON D M Distribution of radioactive cobalt in the rat *Brit J Nutr* 4 (1950) 42
- FISHER J W SANZARI N P BIRDWELL B J and CROOK J J The role of the kidney in erythropoietin production *In Erythropoieses* Edited by L O Jacobson and M Doyle Grune & Stratton New York 1962
- VON HOLT C and VON HOLT L Effect of cobalt and cadmium on the α cells of the islets of Langerhans *Z Naturforsch* 9 b (1954) 319
- HUGGERT A ODEBLAD E SÖRMARK R and ULLBERG S Distribution and kinetics of sodium (Na^{22}) in mice and rabbits *Acta isotopica* 2 (1961), 151
- HULTQUIST G Om mekanismen för koboltkloridverkan på råttor (In Swedish) *Nord Med* 62 (1959), 1686
- KASANEN A LINDGREN I and SALMI H A The accumulation and localization of radioactive cobalt 60 in rat kidney *Acta physiol scand* 61 (1964) 376
- LEE C C and WOLTERINK L T Blood and tissue partition of cobalt 60 in dogs *Amer J Physiol* 183 (1955) 173
- MARSHALL L H Antianemic treatment in experimental polycythemia *Amer J Physiol* 114 (1935) 194
- MEURMAN L and ODEBLAD E Observations on the accumulation of cobalt in rats *Acta haemat* 16 (1956) 400
- NELSON A ULLBERG S KRISTOFFERSSON H and RONNBACK C Distribution of radiocesium in mice An autoradiographic study *Acta radiol* 55 (1961) 374
- ROTHIERY P BELL J M and SPINKS J W T Cobalt and vitamin B_{12} in sheep I Distribution of radiocobalt in tissues and ingesta *J Nutr* 49 (1953) 173
- ULLBERG S Studies on the distribution and fate of S^{35} labelled benzylpenicillin in the body *Acta radiol* (1954) Suppl No 118
- Autoradiographic studies on the distribution of labelled drugs in the body *Second U N Int Conf Peaceful Uses of Atomic Energy* 24 (1958) 248
- KRISTOFFERSSON H FLODIN H and HANNGREN A Placental passage and fetal accumulation of labelled vitamin B_{12} in the mouse *Arch int Pharmacodyn* 167 (1967), 431
- ULRICH F and COPP D H The metabolism of radioactive cobalt (Co^{60}) in normal and alloxan diabetic rats *Arch Biochem Biophys* 31 (1951) 148
- VOLK B W LAZARUS S S and GOLDNER M G Alpha cell damage and blood sugar changes in rabbits after administration of cobalt *Proc Soc exp biol Med* 82 (1953) 406
- WALTNER K and WALTNER K Kobalt und Blut *Klin Wchnschr* 8 (1929) 313

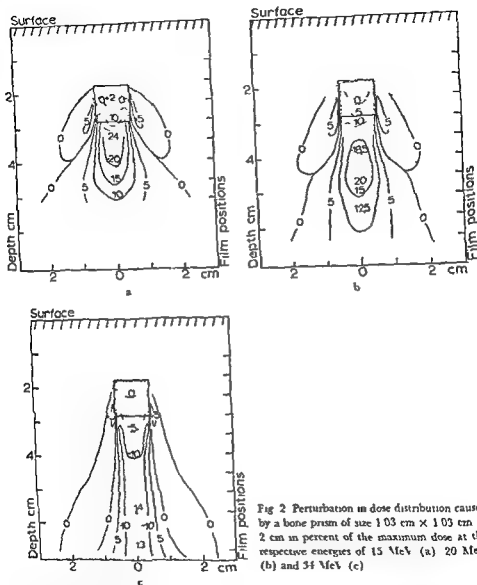


Fig 2 Perturbation in dose distribution caused by a bone prism of size 1.03 cm x 1.03 cm x 2 cm in percent of the maximum dose at the respective energies of 15 MeV (a), 20 MeV (b) and 34 MeV (c)

The resulting density was 1.54 kg/cm³. Bones are actually not homogeneous and for comparison it may be mentioned that the density of the mandible may be of the order of 1.65 g/cm³ (HAAS & SANDBERG 1957).

The perturbation caused by a bone prism of size 1.03 cm by 1.03 cm by 2 cm at primary energies of respectively 15 MeV, 20 MeV and 34 MeV is indicated in

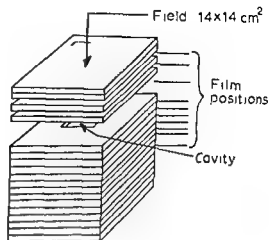
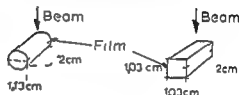


Fig. 1 Polystyrene phantom with a cavity for perturbing bodies (top) and the perturbing bodies introduced in the phantom



Effects of dense structures The dose was measured by means of Kodak M radiographic film. This film has a linear density dose response especially when it is exposed perpendicular to the emulsion plane, which direction was also considered the optimal one for reducing perturbation of the dose distribution from the film itself.

Perturbation of the dose distribution was studied in homogeneous, nearly water equivalent, tissue. The results were made applicable to dose planning by expressing the perturbation in percent of the unperturbed dose at dose maximum. The dose distribution was studied in planes perpendicular to the electron beam at several depths, the films being measured by means of a Joyce double beam micro densitometer. The deviations of the perturbed densitograms from the unperturbed ones were then plotted as illustrated in Figs 2 to 5.

The films were irradiated in a phantom (Fig. 1) placed between polystyrene slabs with a density, ρ , of 1.04 g/cm³ and an effective density, ρ_H , of 0.97 (LOEVINGER, KARZMARK & WEISSBLUTH 1961). A comparison with the corresponding value for perspex (lucite), 1.12, indicates a better equivalency with water.

The perturbing bodies in the soft tissue material (Fig. 1) consisted of bone powder or lead. The bone powder was obtained by milling cattle bones, cooking the powder in water, and drying. The powder was then pressed in steel moulds under high pressure, using a small amount of cellulose lacc as binding agent.

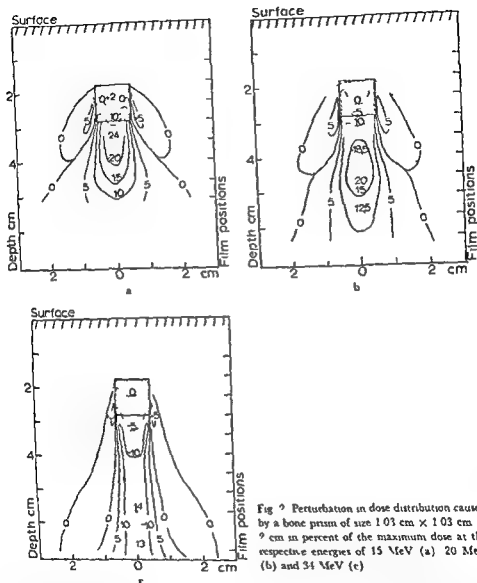


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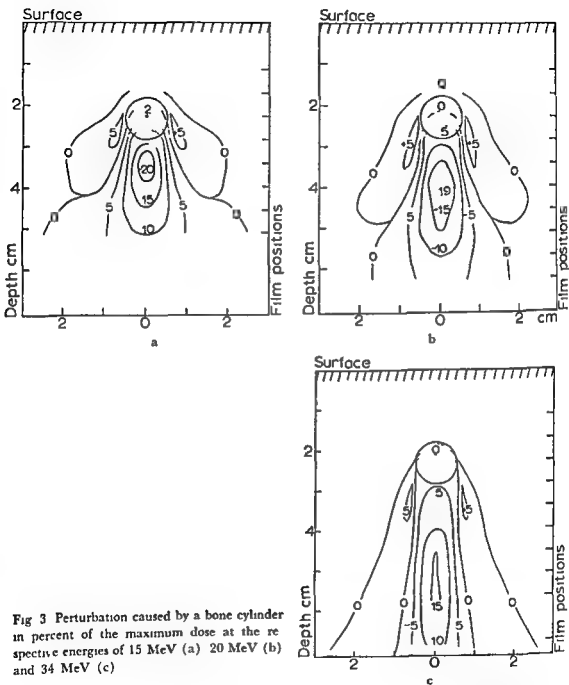


Fig 3 Perturbation caused by a bone cylinder in percent of the maximum dose at the respective energies of 15 MeV (a) 20 MeV (b) and 34 MeV (c)

Fig 2 The distribution is given for a plane cutting the prism perpendicularly in two pieces each of the size 1 cm by 1 cm. The influence of the prism seems to result in two areas of perturbation: (1) a 'shadow area', and (2) a side scatter area.

The explanation for the appearance of area (1) is simple. The radiation

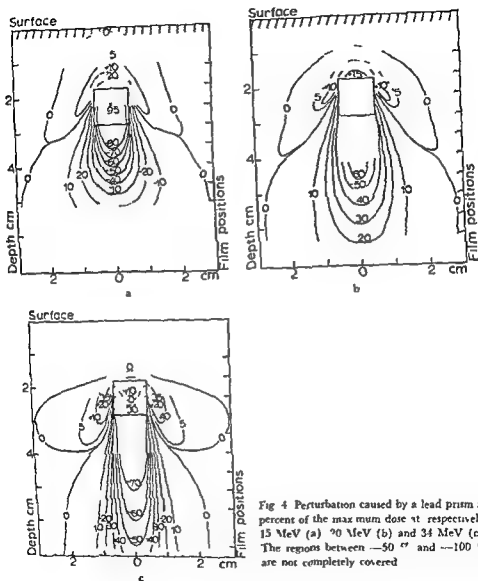


Fig 4 Perturbation caused by a lead prism in percent of the maximum dose at respectively 15 MeV (a) 20 MeV (b) and 34 MeV (c). The regions between -50° and -100° are not completely covered.

entering from the front face of the piece is absorbed (the particles are more or less arrested) in the piece or scattered from the piece resulting in a 'shadow' or a cold volume of low dose. The effect is well known in roentgen and cobalt therapy.

As to the second area of perturbation the radiation scattered from the bone

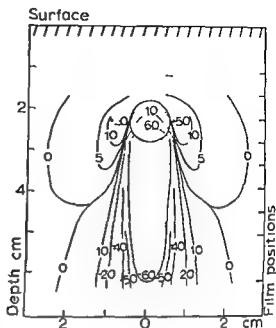


Fig. 2. Perturbation caused by a lead cylinder (cf. fig. 4c).

prism causes an overdose close to the piece. This effect is not so marked with roentgen rays and cobalt radiation but in the case of electrons should be considered as a new phenomenon to be taken into account.

The overdose value does not change with energy, being always between 5 % and 10 %. The underdose, on the contrary, varies between -20 % and -14 % when the energy is increased from 15 to 34 MeV. With increasing energy, the position of the point of lowest dose moves farther from the piece. The volume covered by the shadow reaches far behind the piece at 34 MeV but is shortened at lower energies. The underdose becomes more evident at lower energies.

The perturbation caused by a cylinder of the same material, volume and cross section as the prism was studied in a corresponding manner. The result is recorded in Fig. 3. Excepting error of measurement, the perturbation may be considered to amount to the same value as for the prism, the only significant difference being the shapes of the isodoses close to the piece.

The dose distribution with a lead prism is given in Fig. 4. The electrons do not penetrate the piece at all. The underdose behind the prism is thus approximately 100 % at 15 MeV, 20 MeV, and 34 MeV. Pure scattering from the soft medium is clearly demonstrated and stands for the dose in the shadow, i.e. for the difference between the percentage read in the shadow and 100 % perturbation. The effect of bremsstrahlung from the piece and the machine should be considered, however, if an exact estimate of the pure scattering effect is to be made. The hot spots beside the lead represent a 35 % overdose as com-

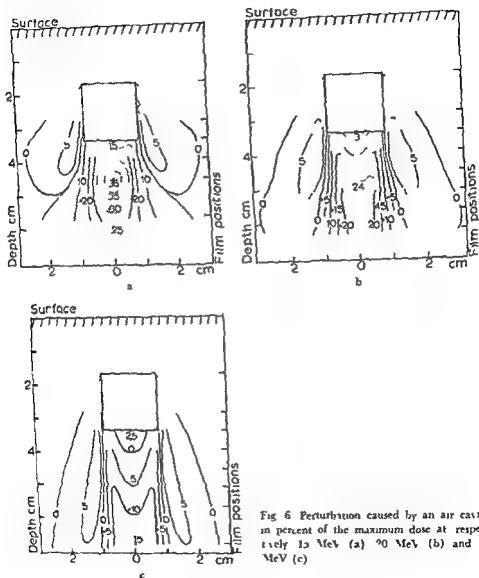
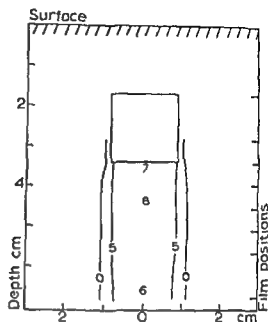


Fig 6 Perturbation caused by an air cavity in percent of the maximum dose at respectively 10 MeV (a) 20 MeV (b) and 34 MeV (c)

pared to only 5 % with bone. Moreover the effect of backscattering is considerable at least at low energies. The geometrical shape may be of some slight influence when the perturbing body is lead (Fig 5).

Effect of cavities Situations of a cavity perturbing the dose distribution may frequently arise in radiation therapy. To simulate the trachea a cavity shaped

Fig 7 Perturbation at cobalt radiation caused by an air cavity in percent of the maximum dose (cf fig 6)



as a long channel of 2 cm by 2 cm cross section was introduced in a polystyrene phantom. Exposure to electrons was performed as previously. The phantom was also exposed to a cobalt beam, to provide a comparison between electron and cobalt beam therapy. The density was measured by an Ansco Macbeth densitometer. The result is illustrated in Fig 6. The perturbation in the two areas is now inverse, compared to the previously investigated conditions. There is now a 'positive shadow' (overdose) due to the absence of absorption in the cavity. The absence of scattering normally produced by soft tissue (now removed) causes an underdose beside the cavity.

No scatter effect at all could be observed with cobalt radiation (Fig 7). The 'positive shadow' is moreover far less marked than that produced by the electrons. Its highest isodose is +35% at 15 MeV electrons and decreases to +15% at 34 MeV. The highest value for cobalt is +8%.

Discussion

Let us now consider the perturbation occurring in the two main cases discussed. There are as mentioned two different areas of deviation with different signs. These are (1) the shadow that is negative in the first case (underdose) and 'positive' in the second (overdose) and (2) the side scattering area characterized by an overdose in the first and an underdose in the second case.

The boundaries of the piece of bone or the cavity define a certain domain in the soft tissue equivalent material. It may now be useful to consider the dose as

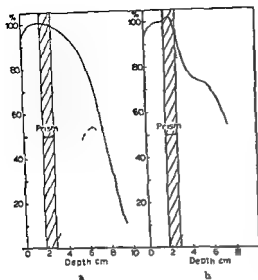


Fig 8 Curves showing the total dose of 20 MeV electrons (solid) unperturbed partial dose (dashed) and zero-perturbed or perturbed dose (dotted) at different depths along the centre line through the domain (a) in a homogeneous phantom and (b) when the domain is filled with the bone prism

caused by two different groups of electrons. One group is made up by perturbed electrons i.e. by primary or secondary electrons having penetrated the perturbing domain or by electrons struck directly or indirectly by them. The energy and direction of the perturbed electrons are related to the type of matter (or void) introduced in the domain. The other group is represented by electrons not having penetrated the domain and not being secondaries of a first or higher generation to perturbed electrons. This group may be called unperturbed electrons. The total dose can accordingly be divided into two parts: the perturbed and the unperturbed partial dose.

The results obtained for lead (Fig 4) enable a study to be made of the unperturbed partial dose at least in the shadow area reached by the unperturbed electrons by scatter from tissue equivalent material surrounding the domain. It may be assumed that only a negligible amount of electrons entering the domain will penetrate parts of the lead piece and scatter to the area behind the domain. Using a common depth dose curve for 20 MeV and the results of Fig 4b we obtain the curves in Fig 8a which apply to a homogeneous case. The solid curve gives the total dose and the dashed curve the unperturbed dose according to Fig 4b. The difference between these two curves (shown dotted) represents the dose due to zero-perturbed electrons or that part of the dose which will be affected when the tissue equivalent material that now fills the domain is replaced by matter of different electron density or void. It should be pointed out that the curves of Fig 8 are related to a domain with the special

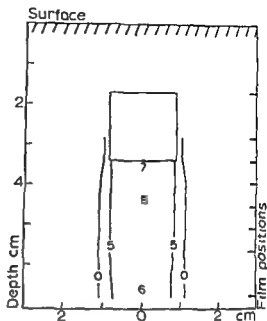


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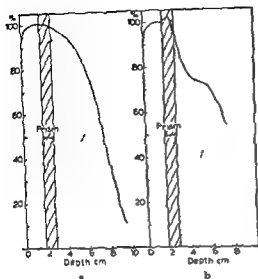


FIG 8 Curves showing the total dose of 20 MeV electrons (solid) unperturbed partial dose (dashed) and zero-perturbed or perturbed dose (dotted) at different depths along the centre line through the domain (a) in a homogeneous phantom and (b) when the domain is filled with the bone prism.

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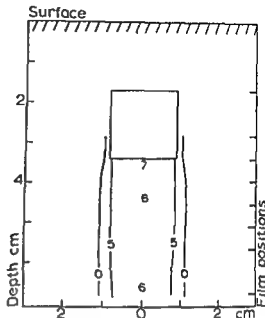


Fig 7 Perturbation at cobalt radiation caused by an air cavity in percent of the maximum dose (cf fig 6)

as a long channel of 2 cm by 2 cm cross section was introduced in a polystyrene phantom. Exposure to electrons was performed as previously. The phantom was also exposed to a cobalt beam, to provide a comparison between electron and cobalt beam therapy. The density was measured by an Ansco Macbeth densitometer. The result is illustrated in Fig 6. The perturbation in the two areas is now inverse, compared to the previously investigated conditions. There is now a positive shadow (overdose) due to the absence of absorption in the cavity. The absence of scattering normally produced by soft tissue (now removed) causes an underdose beside the cavity.

No scatter effect at all could be observed with cobalt radiation (Fig 7). The 'positive shadow' is moreover far less marked than that produced by the electrons. Its highest isodose is +35% at 15 MeV electrons and decreases to +15% at 34 MeV. The highest value for cobalt is +8%.

Discussion

Let us now consider the perturbation occurring in the two main cases discussed. There are as mentioned two different areas of deviation with different signs. These are (1) the shadow that is 'negative' in the first case (underdose) and 'positive' in the second (overdose) and (2) the side scattering area characterized by an overdose in the first and an underdose in the second case.

The boundaries of the piece of bone or the cavity define a certain domain in the soft tissue equivalent material. It may now be useful to consider the dose as

importance. Care should be taken to remember the overdose of 5 % near bone and the underdose of 5 % near a cavity (Figs 2, 3 and 6). If lead is to be used as a shield surrounded by tissue, the strong side scattering effect should also be born in mind. The back scatter in lead is considerable but negligible in bone.

It should be mentioned that the perturbation at an air cavity gives when taken with an opposite sign, the amount of side scattered electrons from the domain when filled with tissue-equivalent material.

It is interesting to consider that the perturbation of the cobalt radiation by a cavity (Fig. 7) is much smaller than the perturbation of electrons. The same results are expected when bone is used as perturbing body.

Acknowledgements

Our thanks are due to Prof. G. Brethling for valuable discussions during the preliminary phase of the investigation and to Prof. E. Tammisalo and Dr. V. Karhuvaara for the opportunity to use the micro-den. nometer at the dental clinic in Åbo.

SUMMARY

The effect of bone and cavities on the dose distribution of electrons was studied on radiographic film at 15, 20 and 34 MeV. Bone and lead pieces of two different shapes and a cavity surrounded by polystyrene were used to simulate anatomical irregularities. The results were compared with similar measurements for cobalt radiation, and the perturbation for electrons was found to be much greater than for cobalt.

ZUSAMMENFASSUNG

Der Einfluss von Knochen und Hohlräumen auf die Dosisverteilung bei Elektronenbestrahlung bei 15, 20 und 34 MeV wurde mittels Röntgenfilm studiert und gemessen. Knochen und Bleistücke von zwei verschiedenen Formen und eine von Polystyren umgebene Hohlraum wurden verwendet, um anatomische Irregularitäten darzustellen. Die Resultate wurden mit den Messresultaten bei Kobaltbestrahlung verglichen und es wurde festgestellt, dass die Störung bei Elektronenbestrahlung größer als bei Kobaltbestrahlung war.

RÉSUMÉ

L'effet des os et des cavités sur la distribution de dose d'électrons a été étudié à 15, 20 et 34 MeV au moyen de films radiographiques avec des morceaux d'os et de plomb de deux formes différentes et avec une cavité entourée de polystyrène pour simuler les irrégularités anatomiques. Les résultats sont comparés avec ceux de mesures semblables faites pour le rayonnement du cobalt. La perturbation de la distribution de dose est bien plus importante pour les électrons que pour le cobalt.

shape of the prism illustrated in Fig. 1. Another domain would give curves of different shapes.

The dotted curve may be considered a depth dose curve for those electrons that have been influenced by the matter in the domain. If matter with a high electron density is introduced, two main effects result. The energy of the zero-perturbed electrons is reduced, and the scattering is increased to give an ensemble of perturbed electrons. The first effect will reduce the range of the curve, and the second will reduce the slope of the curve. The combined effect is seen in Fig. 8b, where the solid line gives the depth dose curve through the bone prism according to Fig. 2b, and the dashed line is the same as in Fig. 8a. The dotted curve again represents the difference or the dose due to the electrons perturbed by the bone prism. The most prominent perturbation of the dose is expected in a region where the zero-perturbed partial dose curve has a steep slope. This is illustrated in Fig. 8. The increase in the distance between the domain and the position of maximum perturbation with increasing energy is therefore understandable.

The perturbation in the shadow area is high enough to be of importance in dose planning. This applies to solid bone as well as to cavities. A calculation of the perturbation is complicated by two facts. First, only a part of the electrons forming the dose is perturbed, as seen above, secondly the depth dose curves of the perturbed electrons depend strongly on the size of the perturbing piece. It is evident that the perturbation on the whole does not depend only on the thickness of the domain but also on its width, which defines the ratio of perturbed and unperturbed electrons. How complicated the situation may be when planning treatments of the head is obvious. Nearly all the electrons are more or less perturbed in some areas when passing bone and cavities of varying thickness and shape. It may however be possible to find approximate methods to calculate the dose in areas of such complex structure (LAUCHLIN 1966).

The present results indicate that the maximum value of perturbation decreases with increasing energy. This is true for bone and air cavities. At lower energies the mean scattering angle is larger, facilitating the scattering of unperturbed electrons on to the shadow area, this is expected to increase the relative importance of the unperturbed electrons in forming the dose at the cost of the contribution of perturbed electrons. At lower energies, however, the change in the depth dose curve for the zero-perturbed group by the introduction of perturbing matter (or void) will influence an area that lies closer to the domain than the region reached by the bulk of unperturbed electrons. The perturbed electrons in this area will dominate the dose to give the more marked perturbation observed at lower energies.

The results clearly indicate that the perturbation at the side area is of minor

importance. Care should be taken to remember the overdose of 5 % near bone and the underdose of 5 % near a cavity (Figs 2, 3 and 6). If lead is to be used as a shield surrounded by tissue the strong side scattering effect should also be born in mind. The back scatter in lead is considerable but negligible in bone.

It should be mentioned that the perturbation at an air cavity gives when taken with an opposite sign the amount of side scattered electrons from the domain when filled with tissue-equivalent material.

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L'effet de os et des cavités sur la distribution de dose d'électrons a été étudié à 15, 20 et 34 MeV au moyen de films radiographiques avec des morceaux d'os et de plomb de deux formes différentes et avec une cavité entourée de polystyrène pour simuler les irrégularités anatomiques. Les résultats sont comparés avec ceux de mesures semblables faites pour le rayonnement du cobalt. La perturbation de la distribution de dose est bien plus importante pour les électrons que pour le cobalt.

REFERENCES

- BREITLING G und VOGEL K H Dosisverteilung bei der Bestrahlung inhomogener Medien mit schnellen Elektronen *Strahlentherapie* 122 (1963), 321
- HAAS L L and SANDBERG G H Modification of the depth dose curves of various radiations by interposed bone *Brit J Radiol* 30 (1957), 19
- LAUGHLIN J S Symposium on Megavoltage radiation therapy and high energy electron therapy 'Madrid September 1966
- LOEVINGER R, KARZMARK C J and WEISBLUTH M Radiation therapy with high energy electrons *Radiology* 77 (1961), 906
- NETTELAND O *Isodose measurements in inhomogeneous matter Symposium on high energy electrons* p 116 Proceedings Edited by Zuppinger A and Poretti G Springer Verlag Berlin 1965

THRESHOLD DOSES FOR CONDITIONED AVOIDANCE BEHAVIOR USING LOW DOSE RATE GAMMA RADIATIONS

by

H LEVAN R HAAS H SASSOON and F KROWN

During the past decade many results have been reported on various aspects of postirradiation saccharin aversion in mice. It is well known that mice prefer saccharin sodium solution to tap water and avoid this solution after being exposed to ionizing radiations. Many techniques have been used with roentgen and gamma rays and fast neutrons (GARCIA & KIMELDORF 1960) to condition saccharin aversion. No explicit investigations however have been done for threshold doses or dose rates for saccharin aversion conditioning. In this paper we are presenting results from our recent studies of some threshold doses using both saccharin and sucrose as the conditioned stimuli and gamma radiations with extremely low dose rates as the unconditioned stimulus.

Method Sixty CFW male mice 50 to 60 days old were used. The animals were randomly divided into two groups each composed of three cages with 10 mice in a cage and maintained in a controlled temperature room. The cages (30 cm long \times 20 cm wide \times 14 cm high) were made of 3 cm thick lead.

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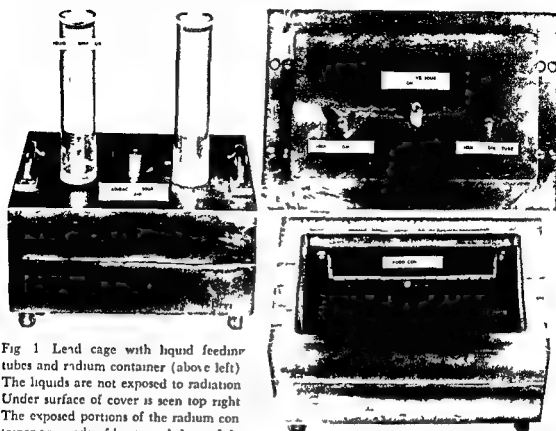


Fig 1 Lead cage with liquid feeding tubes and radium container (above left) The liquids are not exposed to radiation Under surface of cover is seen top right The exposed portions of the radium container are made of lucite and those of the liquid feeding tubes are made of aluminum Interior view of the cage is seen to the right in the figure

(Fig 1) The removable top of each cage has three holes to accommodate the liquid feeding tubes on the right and the left side, and the radioactive container in the middle. The under surface view of the cover is seen to the right in the figure (top). The lucite liquid feeding tubes containing either saccharin sodium solution or sucrose solution on one side and plain tap water on the other side were graduated in cubic centimeters. These tubes were alternated daily to compensate for any possible positional preference. Purina food pellets were available at all times in a food basket mounted inside each cage. The bottom of the cage was made of a stainless steel screen for ventilating purpose. The cage bottom, supported by four 5 cm high copper legs, was separated from the ground by an air gap. Those parts of the liquid feeding tubes that are seen in the figure extend 3 cm into the cage and the part seen of the radioactive source container extends 6 cm into the cage. A 5 mg radium capsule was used as source.

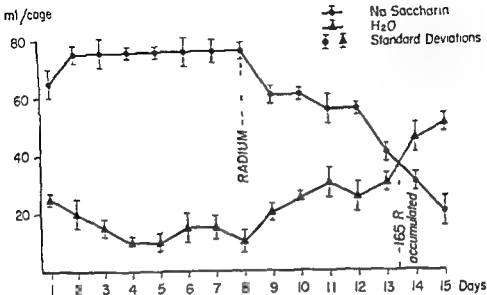


Fig 2 H₂O and Na saccharin consumption before and after the introduction of radium source to the cage

Dosimetry was performed using the energy storage and thermoluminescent response of lithium fluoride embedded in a teflon matrix. The matrix was formed into a rod 1 mm in diameter and 6 mm in length. These rods were embedded under the skin on the back of each mouse before initiation of the preference test and removed for reading when the mouse was sacrificed at the end of the experiment. They were then read on a Controls for Radiation Model 3100 Thermoluminescent Reader. The resultant doses were averaged to indicate the average total exposure and by inference the average exposure dose rate in the cage. The reader and rods were calibrated to read radium gamma exposure rates in air. Each experimental part with three cages of mice containing ten each was run under the same conditions except that the liquids used were different: saccharin sodium solution (1 % of weight) was offered to the first group and sucrose solution (5 % of weight) to the second. After a short period of rest and getting settled in the new environment the mice showed definite preference of either saccharin or sucrose. The radium capsule was then inserted into the container. The dose rate emitted by this source was approximately 2.1×10^{-4} R/min (at an average distance of 6 cm between the source and the mice).

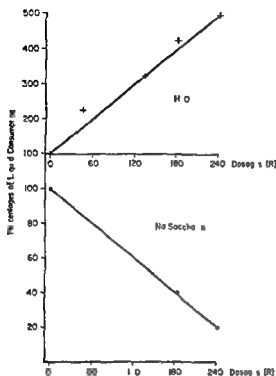


Fig 3 Gamma ray dosages versus percentage of H₂O and Na saccharin consumption

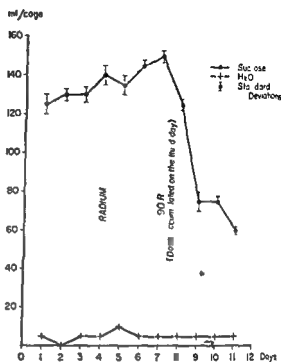


Fig 4 H₂O and sucrose consumption before and after the introduction of the radium source

Results and Discussion

Saccharin sodium solution was used in the first experimental part. Eight days after the initiation of the taste preference test (Fig 2), the mice definitely preferred this sweet solution to tap water. The radium source was then deposited in the container. On the following day, the data recorded indicated an average decrease of some 15 ml in the daily amount of saccharin consumed, and an average increase of 10 ml in that of water. This trend was observed until between the 13th and 14th day of the experiment (5.5 days after the introduction of the radium capsule) when the average daily water consumption surpassed that of saccharin sodium. At this time the mice had been exposed to approximately 165 R of gamma radiations. On the 15th day, this experimental part was terminated. The average increase in daily water intake was then 40 ml from the time the radium capsule was introduced to the cage. The average decrease in daily saccharin consumption was 55 ml lower than at the start. The consumption versus average exposure is recorded in Fig 3. Approximately 210 R were ac

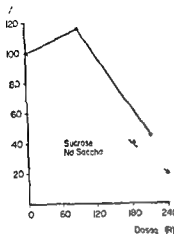


Fig. 3 Gamma ray dosages versus percentages of liquid (sucrose and its saccharin) intake

accumulated during this experiment. On the day the radium capsule was introduced into the cage the average daily water and saccharin consumption were scored as 100%. At the end of the experiment the saccharin intake dropped to 20% while that of water increased to 500%.

As may be seen from the curves the changes in liquid consumption are rather linear. It is quite difficult to establish the precise starting point of avoidance of saccharin solution and the accumulated radiation dose at that time. In a minute by minute analysis of water and saccharin preferences following simultaneous exposures to saccharin and gamma rays SMITH & SCHAEFFER (1966) found that the aversion started within 15 minutes after exposures. We can only say that with the extremely low dose rate used in this experiment the threshold dose for saccharin aversion was much less than 30 R. Between the 2nd and the 4th day after the mice were exposed to radiation there was a recession in the daily drop of saccharin consumption perhaps at this low dose rate and after sensing radiation on the 1st day the animals tolerated the new conditions for a while before it became unbearable on the 4th day (150 R accumulated). GARCIA et coll (1955) using saccharin solution (0.1% of weight) reported that 6 hour exposure to 30 R (^{60}Co /gamma rays) produced a conditioned aversion to saccharin solution and 57 R produced an absolute rejection of this solution. According to SMITH et coll (1964) the duration of exposure for a successful conditioning was about 7 seconds (100 R of roentgen rays). At this rate being well above threshold level these investigators found that the same high degree of aversion was produced (exposure rate was between 100 R to 828 R/min). Our results indicated that at extremely low dose rates (0.02 R/min) 100 R of

gamma radiation produced a drop of some 35 % in the average daily saccharin intake and an increase of 175 % in the daily water consumption.

For sucrose solution (5 % of weight), the results were somewhat different (Fig. 4). The preference of sucrose to water was much higher as compared with saccharin. The same radium capsule was deposited in the container 4 days after the initiation of the sucrose taste preference test. Only negligible changes were observed in both water and sucrose consumptions on the next day. The mice continued with preference for sucrose solution until the end of the 3rd day, corresponding to an exposure of approximately 90 R. On the next two following days, the average daily sucrose intake decreased by 50 % (from 150 ml to 75 ml). This experiment ended one week after the radium capsule had been introduced into the cage.

Compared to the results obtained in the first experimental part, we found that while the avoidance of saccharin solution was observable within only one day of exposure that of sucrose took much longer. At this extremely low dose rate, the mice avoided sucrose solution only after they had been exposed to 90 R of gamma radiation (Fig. 5). Thereafter, the drop in the percentage of the sucrose consumed was almost linear with the doses accumulated. The average daily intake remained unchanged. Sodium saccharin has been reported to be about 675 times as sweet as sucrose (MONGRIEFF 1944), the solution used in our experiment was then estimated to be about 135 times as sweet as the sucrose solution. This raises a question whether the degree of sweetness of the solution employed is a factor in this conditioned avoidance behavior. Our results seemed to show that the sweeter the solution, the faster could conditioning be produced. It is interesting to note that the average daily water consumption did not change significantly in the sucrose experiment while it appeared to be a linear function of dose in the saccharin experiment.

Acknowledgements

We wish to thank Prof. Roger A. Harvey for his special interest in our project and Prof. Walter S. Moos for his many valuable viewpoints.

SUMMARY

When mice are exposed to low dose rate gamma radiations (2×10^{-4} R/min) the threshold dose for the conditioned aversion to 1 % saccharin sodium solution is much less than 30 R and for aversion to 5 % sucrose solution is about 90 R. The degree of avoidance changes with the sweetness of the solution and is a linear function of the accumulated radiation dose.

ZUSAMMENFASSUNG

Mäuse wurden mit sehr niedrigen Dosen von Gammastrahlen (2×10^{-2} R/min) irradiert. Die Schwellendosis für ihre bedingte Aversion gegen eine 1 prozentige Na Saccharinlösung war viel geringer als 30 R und die für Aversion gegen eine 5 prozentige Saccharose Lösung ungefähr 90 R. Der Abstinenzgrad wechselt mit der Susse der Lösung und ist eine lineare Funktion der akkumulierten Bestrahlungsdosis.

RÉSUMÉ

Quand des souris sont exposées à de très faibles débits de dose de rayonnement gamma (2×10^{-2} R/min) la dose seuil pour l'aversion conditionnée à une solution de sel de sodium de la saccharine est très inférieure à 30 R, et celle qui conditionne leur aversion pour une solution de saccharose à 5 % est d'environ 90 R. Le degré d'aversion varie avec la douceur de la solution et est une fonction linéaire de la dose totale de rayonnement.

REFERENCES

- GARCIA J. and KIMMELDORF D. J. Conditioned avoidance behavior induced by low-dose fast neutron exposure. *Nature* 185 (1960) 261.
- — and KOELLING R. A. Conditioned aversion to saccharin resulting from exposure to gamma radiation. *Science* 122 (1955) 157.
- MONCRIEFF H. W. *The chemical senses*. Wiley, New York 1944.
- SMITH J. G. and SCHAEFFER R. W. A minute by minute analysis of water and saccharin preferences following simultaneous exposures to saccharin solution and gamma rays. Paper presented at the 14th Annual Meeting of the Radiation Research Society, Coronado, California, February 13—16, 1966.
- MORRIS D. D. and HENDRICKS J. Conditioned aversion to saccharin solution using high dose rates of X rays as the unconditioned stimulus. *Radiat. Res.* 22 (1964) 507.

HUMAN RADIUM ASSAY AT NANOCURIE LEVELS USING EXTERNAL COUNTING OF LOW ENERGY PHOTONS

by

L. G. BENGTSSON

Many gamma rays are emitted in the decays of ^{226}Ra and its daughters. When these nuclides are present in a human subject, the gamma rays, as measured by whole body counting, will be distorted by scattering and absorption within the human body. As a result, the spectrum obtained will be very complex and similar to the spectrum in Fig. 1. This spectrum was obtained from measurement of a ^{226}Ra source in the middle of a masonite phantom, using a NaI(Tl) crystal. There are some prominent peaks in this spectrum which are often used for detection of radium in man, especially the one around 1.76 MeV (FLANS 1965, PSZONA, ADAMSKA & ZARNOWIECKI 1963, WENGER & MILLER 1963). In the present investigation it has been found that the low energy region of the spectrum may also be used to advantage for detection of radium in man. This article thus presents one of several attempts made by whole body counting investigators in recent years to make more efficient use of the information contained in the entire spectrum (MCNEILL & MOHINDRA 1964, LILLEGRAVEN & RUNDO 1965, BENGTSSON 1964).

An indication of the usefulness of the various energy ranges of radium spectra for an assay of small amounts of radium has been obtained from a consideration

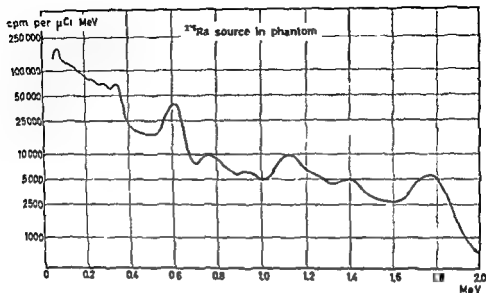


Fig 1 Spectra from a masonite phantom containing a ^{226}Ra source Scanning bed geometry and $20\text{ cm} \times 20\text{ cm}$ NaI (Tl) crystal

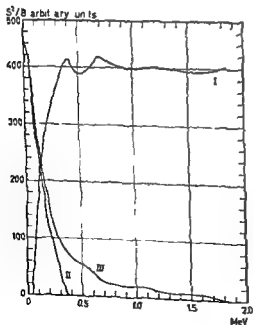


Fig 2 Figure of statistical merit S/B (the same arbitrary units as in Table I) for the various parts of a spectrum similar to the radium spectrum obtained in man. S/B was calculated for energy angles within 1 m fixed and the other set as indicated by the reading on the horizontal axis. The energy ranges are then: I—lower limit 0.04 MeV , upper limit variable; II—lower limit variable, upper limit 0.38 MeV ; III—lower limit variable, upper limit 1.87 MeV .

Table 1

Influence of the chosen energy range on the counting statistics for assay of small amounts of radium in an otherwise radioactivity free subject (Compare also Fig. 2) S = counting rate from radium, B = background counting rate figure of merit S/B (the same arbitrary units as in Fig. 2)

Principal gamma energy MeV	Energy range MeV	S/B arbitrary units	Minimum detectable amount of radium relative to energy range 0.04 to 0.11 MeV
—	0.04—0.38	410	1
0.609	0.52—0.72	30	3.7
1.12	1.02—1.18	7	7.6
1.76	1.60—1.82	10	6.4

of counting statistics. There are some differences between the phantom spectrum in Fig. 1 and the spectrum from ^{226}Ra in man because of the disequilibrium with the daughter products in the latter case (about 2/3 of ^{226}Ra escape from the body) and because of the self absorption of soft gamma rays in bone. The results derived from the statistical considerations below will only in details be influenced by such differences. The statistical merit for various energy ranges has been calculated for spectra similar to the one shown in Fig. 1. As a figure of merit S/B has been used, where S is the net counting rate from radium and B is the background counting rate. This figure of merit applies to the hypothetical case of a subject free of any radioactivity other than an amount of radium so small that S will be much smaller than B . Results from the calculations are given in Fig. 2 and Table 1. Some care should be exercised in the application of these results to man because the spectrum below 100 keV may vary considerably, among other things because of the absorption in bone of the low energy gamma rays. It is nevertheless quite evident that the statistical merits of the low energy region of the spectrum are considerable. Much smaller amounts of radium can be detected than by the use of the higher peaks for the hypothetical situation treated.

Man is in fact not free from radioactivity but contains various radionuclides, mainly ^{137}Cs from fall out and a natural potassium burden including ^{40}K . The total counting rate from these radionuclides in the low energy end of the spectrum is of the same order of magnitude as the background counting rate. For some parts of the spectrum S/B as given in Fig. 2 and Table 1 would then be changed by about a factor of 2 for a subject containing about 15 nCi ^{137}Cs and 100 g potassium, but the advantages to be expected from use of the low

energy region would persist. The possible usefulness of the suggested low energy region is however limited by the accuracy with which we can account for the contributions from ^{137}Cs and potassium in the individual case. In fact, since the background in the low energy region varies with the size of the subject we must also be able properly to estimate the contribution from the background to the subject's gross spectrum. The treatment of these problems is described below.

Equipment and Methods The whole body counter in these measurements has been described in the Directory of Whole Body Radioactivity Monitors (IAEA 1964). The scanning took place in a steel room using a NaI(Tl) crystal of 20 cm diameter and 10 cm length with 45 cm bed crystal distance and a scanning length of 144 cm. The subject is as a rule measured 19 min in the prone as well as 19 min in the supine position. The average result from the two measurements has been used in this work. Pulse height spectra were recorded with a 200 channel analyser (RIDL model 34-8) and punched on paper tape. Computations were made on the SMTL computer at Lund.

The experimental work has proved the necessity of taking utmost care to avoid disturbances from various sources. Each subject had a shower and a hair wash before each measurement and was dressed in a cotton overall during the measurement. The overalls were checked for activity content and only uncontaminated overalls were used. Measurements of the background were performed before and after each measurement in the subject, and significant changes were found in the low energy region of the background spectra. These changes seemed to be slow and it took hours before they appeared or disappeared. The door of the steel room was only left open for passage in and out which may have served to diminish the variations.

Calibration studies of the influence of body weight on the spectra from ^{137}Cs and ^{40}K have been reported by BENGTSSON (1964). A linear relation was assumed to exist between the ratio (low energy band counting rate)/(peak counting rate) and the body weight. A linear relation was also found for the dependence of the background in the low energy band on body weight. An estimate of the sensitivity for radium distributed in the skeleton was made through calibration studies of a ^{226}Ra source in different positions in masonite phantoms of varying size and shape. This estimate proved to be in reasonable agreement with the results from other laboratories in an intercomparison study of two subjects containing ^{226}Ra (WENGER, BENGTSSON, DUDLEY et al.). It is important to note that the source (NBS standard source No. 4956) contained ^{226}Ra in solution in a sealed ampoule. For the low energy end of the spectra the usual platinum encapsulation of radium sources caused heavy absorption and even

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Influence of the chosen energy range on the counting statistics for assay of small amounts of radium in an otherwise radioactivity free subject (Compare also Fig 2) S = counting rate from radium B = background counting rate figure of merit S^2/B (the same arbitrary units as in Fig 2)

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Table 2

Detectability of radium according to measurements on subjects containing 70 to 160 g of potassium and 5 to 20 nCi ^{137}Cs . The subjects were each measured 38 min. Background was measured during 39 min before and 38 min after the subject measurement. SD = standard deviation.

Criterion for detectability	Detectable ^{226}Ra nCi		nCi ^{226}Ra corresponding to observed average test	
	Using 0.04 to 0.40 MeV	Using 1.60 to 1.83 MeV	0.04 to 0.40 MeV	1.60 to 1.83 MeV
3 SD from counting statistic	1.0	2.9		
3 SD from observed rest counting rate all weights (20 subjects)	1.6	2.9	1.0	0.5
3 SD from observed rest counting rate weight 53–67 kg (8 subjects)	1.1	1.3	0.8	0.5

0.1 nCi ^{226}Ra which gives 1 cpm). For comparison the corresponding data for the energy range 1.60 to 1.82 MeV is given in Fig. 3b.

The magnitude of the rest counting rate is however less interesting than the fact that the spread of the individual rests about the average rest value is not much greater than that which could be expected from counting statistics (see Table 2). This means that there should be an advantage using the low energy band to decide which people have a radium burden below the detectable. This was also demonstrated through measurements of two subjects contaminated with small amounts of radium (BERG, KRISTENSEN, GRANDE & MADSEN 1966). These subjects were measured in chair geometry four times with approximately half year intervals. Their radium contents could be predicted from the chair geometry retention curves when they were too small to be measured from the 1.76 MeV peak. This peak like most gamma rays does in fact originate not from ^{226}Ra but from ^{214}Bi which is a decay product in the ^{226}Ra series. There is one weak gamma ray from ^{226}Ra at 0.19 MeV which should contribute about 10 per cent of the total counting rate in the range 0.04 to 0.40 MeV. For this application it can be disregarded and what is really assayed by gamma spectrometry is thus ^{214}Bi and other ^{226}Ra series nuclides in equilibrium with ^{214}Bi so body burdens are given for ^{214}Bi only. The ^{226}Ra body burden is usually three times higher than the ^{214}Bi burden. The relevant results of measurements of radium contaminated subjects are given in Fig. 4. The histograms from Fig. 3 have been reproduced on the axes for rest counts.

For detection of small amounts of radium in a control group we should specify a detection level of rest counting rate. Subjects with rest counting

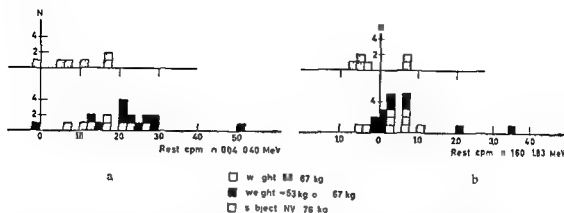


Fig. 3 Frequency distributions of rest counting rates for 38 min measurements in 20 normal subjects and for six 38 min measurements in subject NV. N = number of subjects with rest counting rate within a given interval. a) Low energy band 0.04 to 0.40 MeV. b) 1.76 MeV peak 1.60 to 1.83 MeV.

the available radium sources on thin silver foil (Amersham RAM 2) were not suitable for the calibrations because of too high absorption in the silver.

The evaluation of the usefulness of the low energy range for the assay of radium in human subjects has been made in two ways.

1 It is possible to extend the common procedure for assay of ^{137}Cs and potassium in human subjects to include a detection procedure for radium. Additional to the ^{137}Cs and potassium energy ranges, a low energy range is included. In this energy range, the individual contributions from the ^{137}Cs and potassium energy ranges are subtracted using a spectrum stripping procedure. If the remaining rest is too large, a further investigation may reveal whether the rest is caused by radium.

2 When it is known that a radium contamination is present, the calculations include also the contributions from radium in the ^{137}Cs and potassium energy ranges.

Results

1 *No radium contamination assumed* A group of subjects from Lund (55° 7' N, 13° 2' E) were measured and the results from the calibration studies were used to subtract from each subject's gross spectrum the contributions in the low energy band (40 to 400 keV) from his ^{137}Cs , ^{40}K and background. On the average, the rest obtained (Fig. 3a) was a little more than zero. This may be due to inaccurate corrections for the various contributions in the gross spectrum, and also to small amounts of unknown radioactivity (for instance adult Swedish subjects should contain about 1 nCi ^{90}Sr which gives 0.6 cpm, and

Table 2

Detectability of radium according to measurements on subjects containing 70 to 160 g of potassium and 5 to 20 nCi ^{137}Cs . The subjects were each measured 38 min. Background was measured during 38 min before and 38 min after the subject measurement. SD = standard deviation.

Criterion for detectability	Detectable B nCi		nCi B corresponding to observed average rest	
	Using 0.04 to 0.40 MeV	Using 1.60 to 1.83 MeV	0.04 to 0.40 MeV	1.60 to 1.83 MeV
3 SD from counting statistics	1.0	2.9		
3 SD from observed rest counting rate (11 weights (20 subjects))	1.6	2.9	1.0	0.5
3 SD from observed rest counting rate weight 53—67 kg (8 subjects)	1.1	1.3	0.8	0.5

0.1 nCi ^{226}Ra which gives 1 cpm). For comparison the corresponding data for the energy range 1.60 to 1.82 MeV is given in Fig. 3b.

The magnitude of the rest counting rate is however less interesting than the fact that the spread of the individual rests about the average rest value is not much greater than that which could be expected from counting statistics (see Table 2). This means that there should be an advantage using the low energy band to decide which people have a radium burden below the detectable. This was also demonstrated through measurements of two subjects contaminated with small amounts of radium (BERG, KRISTENSEN, GRANDE & MADSEN 1966). These subjects were measured in chair geometry four times with approximately half year intervals. Their radium contents could be predicted from the chair geometry retention curves when they were too small to be measured from the 1.76 MeV peak. This peak like most gamma rays does in fact originate not from ^{226}Ra but from ^{214}Bi which is a decay product in the ^{226}Ra series. There is one weak gamma ray from ^{226}Ra at 0.19 MeV which should contribute about 10 per cent of the total counting rate in the range 0.04 to 0.40 MeV. For this application it can be disregarded and what is really assayed by gamma spectrometry is thus ^{214}Bi and other ^{226}Ra series nuclides in equilibrium with ^{226}Ra so body burdens are given for ^{226}Ra only. The ^{226}Ra body burden is usually three times higher than the ^{214}Bi burden. The relevant results of measurements of radium contaminated subjects are given in Fig. 4. The histograms from Fig. 3 have been reproduced on the axes for rest counts.

For detection of small amounts of radium in a control group we should specify a detection level of rest counting rate. Subjects with rest counting

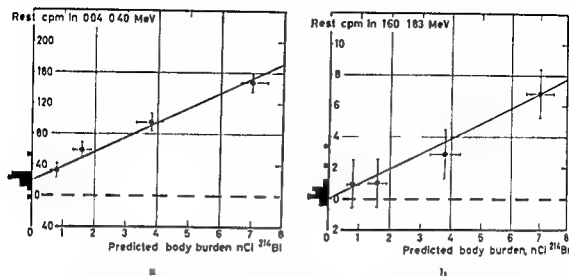


Fig. 1. Rest counting rates for two subjects with slight contamination of radium. Calculation was made as in fig. 3. bars indicate ± 2 SD. a) Low energy band 0.04 to 0.40 MeV. b) 1.76 MeV peak 1.60 to 1.83 MeV. The subjects were measured in the scanning bed geometry.

rates below this level should be assumed to have no detectable radium content. Those having a rest counting rate above the specified level should be assigned a radium content and this content should be checked by further measurements. The choice of the detection level is somewhat arbitrary. Whether we chose for this level the average rest value plus three standard deviations expected from counting statistics or plus three standard deviations as estimated from the spread of the observed rest values, comparison of the two energy ranges shows that the detectability is better by a factor of between 2 and 3 for the low energy range (Table 2).

The rest counting rate in the low energy range was 50 cpm for one subject (Fig. 3a), although the counting rate in the 1.76 MeV energy range was negative. This subject was remeasured after one month. The rest counting rate in the low energy range was this time 10 cpm which is more consistent with the distribution of the other rest values in Fig. 3a.

The spread of the observed rest counting rate is apparently reduced if the weights of the subjects are restricted to a narrow weight range. This might be due to a more correct subtraction of contributions from ^{137}Cs and potassium for these weights (the Alderson phantom used for medium weights might be more reliable than the home made bottle phantom used for higher and lower weights (see BENGTSSON 1961). However, it may be doubtful to subgroup results from only 20 cases, and for the energy range 1.60 to 1.83 MeV, the results from the medium weight group happen to be far too well gathered.

Table 3

Comparison of results from assay of small human body burdens of ^{226}Ra using an energy range between 0.04 and 0.40 MeV and an energy range around the 1.76 MeV peak (1.60 to 1.82 MeV). Subjects were measured 76 min and background was measured 38 min before and 38 min after the subject measurement. SD stat = standard deviation from counting statistics. SD syst = estimated systematic standard error from calibration uncertainties.

Subject cod height and weight	Date of measurement	Energy range 0.04 to 0.40 MeV			Energy range 1.60 to 1.82 MeV		
		Body burden	nCi	\pm B	Body burden	nCi	B _i
			SD stat	SD syst		SD stat	SD syst
HP 156 cm 57 kg	16.11.65	6.4	0.23	0.29	6.5	0.83	0.93
141 160 cm 63 kg	20.7.66	3.7	0.22	0.17	2.7	0.80	0.09
	16.11.65	2.0	0.92	0.09	1.0	0.78	0.04
	20.7.66	1.1	0.90	0.03	0.9	0.78	0.03

2. *Radium contaminated subjects* It should be observed that for the type (1) analysis of the subjects containing radium no assumption was made concerning radium content. Thus the counts from radium in the cesium and potassium peaks were treated as had they been due to these latter nuclides. There is consequently a loss of information which contributes to the impairment of the statistical merit discussed on page 150. Some of this merit can be regained if we approach the problem of estimating the contamination of a subject, knowing that he has a radium content. In this case the contributions in the cesium and potassium ranges are made equal to zero and those in the low energy band are equalled to the average rest for normal subjects. From the results given in Table 3 it is apparent that the statistical accuracy for low radium contents is much improved by use of the low energy band. Instead however the systematic errors due to variations in the shape of the human radium spectrum are somewhat larger than for the high energy band. These errors have been estimated from phantom measurements. A further source of error is the uncertainty of the true rest counting rate. We may assume that the observed individual rest counting rates are the result of counting statistics variations around one common rest counting rate. For the whole normal group this common rest counting rate in the energy range 0.04 to 0.40 MeV then corresponds to 1.0 ± 0.1 nCi ^{226}Ra . For the intermediate weight group the corresponding figure is 0.8 ± 0.1 nCi. In each case the standard error of the mean rest counting rate thus corresponds to 0.1 nCi ^{226}Ra . For the energy

range 1.60 to 1.82 MeV the corresponding figure is 0.2 nCi ^{14}Bi . The assumption used is not self-evident for the energy range 0.04 to 0.40 MeV, but can only be checked through measurement of a considerably larger control group.

Discussion

The content of ^{226}Ra in man on the average amounts to less than 0.1 nCi (STEINNEY 1960). This content originates from the intake of radium through various channels. There are large variations in the naturally occurring radium levels, for instance in drinking water. As a consequence, individuals exist with natural body burdens slightly smaller than 1 nCi ^{226}Ra (STEINNEY) and even higher body burdens may be possible. The limit of detectability of ^{226}Ra in humans is with conventional whole body counting methods very approximately 5 nCi (EVANS 1965, PSZONA *et al.* 1963, MUTH & OBERHAUSEN 1964, VENNART, MAYCOCK, GODFREY & DAVIES 1964, BOULENGER, COLARD & HENRY 1962). Natural radium burdens could probably be detected by means of whole body counting in an increasing number of people if this limit were lowered.

The results of the present work show that the detectability of radium in individuals with cesium body burdens up to about 20 nCi ^{137}Cs can be improved by about a factor of 2 by use of the energy band from 40 to 400 keV as compared to a band covering the 1.76 MeV peak. The accuracy for assay of small amounts of radium can also be improved in this way but the results do not allow conclusions as to the exact magnitude of the improvement. The comparison has not been made for the prominent 0.61 MeV radium peak which lies so close to the 0.66 MeV ^{137}Cs peak that the systematic errors associated with its use would be severe.

It should be observed that these measurements are made in scanning geometry where the spectral variations from subject to subject should be easier to evaluate than, for instance, in the more sensitive chair geometry. However, results from analysis of chair geometry measurements indicate that the improvement may persist also for this geometry (DEVELL, VENNERT and MANDARIL 1966).

Acknowledgement

The author wishes to thank Professor Kurt Lidén for his advice and encouragement during this investigation.

SUMMARY

The sensitivity of whole body counting (NaI(Tl) crystal) for assay of small amounts of ^{226}Ra can be increased by special use of the low energy part of the spectrum. For normal subjects the minimum detectable amount of the ^{226}Ra daughter ^{214}Bi can be improved by

about a factor of 2. This was verified from measurements of both 20 normal subjects containing besides potassium also 5 to 20 nCi ^{137}Cs and two subjects containing also 1 to 6 nCi ^{214}Bi (normally equivalent to about 3 to 20 nCi ^{226}Ra). Since the identification obtained from the low energy part of the spectrum is poor the main use of the method will be for sorting out members of a given group not containing any detectable amounts of radium.

ZUSAMMENFASSUNG

Die Empfindlichkeit eines Ganzkörperzählers zum Nachweis geringer Mengen von ^{226}Ra kann durch eine spezielle Auswertung des niederenergetischen Teils des Spektrums verbessert werden. Für den Normalmenschen wird der minimale anzeigbare Beitrag des Tochterproduktes ^{214}Bi von ^{226}Ra um einen Faktor 2 herabgesetzt. Das wird sowohl durch Messungen an 20 Normalmenschen, die neben K ebenfalls 1–6 nCi ^{137}Cs enthielten, bestätigt als auch an 2 Personen, die ausserdem noch einen Gehalt von 1–6 nCi ^{214}Bi (normalerweise äquivalent 3–20 nCi ^{226}Ra) hatten. Da die Identifizierung mit Hilfe des niederenergetischen Teils des Spektrums schlecht ist, ist die Methode hauptsächlich dafür geeignet, aus einer Gruppe von Menschen solche auszusondern, die keine nachweisbaren Mengen von Ra enthalten.

RÉSUMÉ

La sensibilité du comptage corporel total (cristal de NaI(Tl)) pour la mesure de petites quantités de ^{226}Ra peut être augmentée si on utilise spécialement la partie du spectre qui a une faible énergie. Pour les sujets normaux la plus petite quantité décelable de ^{214}Bi élément fils de ^{226}Ra peut être réduite environ par un facteur 2. Ceci a été vérifié par des mesures effectuées sur 20 sujets normaux contenant outre de potassium de 5 à 20 nCi de ^{137}Cs et sur deux sujets contenant aussi de 1 à 6 nCi de ^{214}Bi (équivalent normalement à 3 à 6 nCi de ^{226}Ra). Étant donné que l'identification par la partie du spectre qui a une faible énergie est mauvaise la principale utilité de cette méthode sera de reconnaître dans un groupe donné les sujets qui ne contiennent pas de quantité décelable de radium.

REFERENCES

- BENGTSSON G. Human beta bremsstrahlung detection by means of thin and thick sodium iodide crystals. In: Assessment of radioactivity in man Vol I p. 91 IAEA Vienna 1964.
- BERG O., KRISTENSEN K., GRANDE P. and MADSEN C. II. A radium accident in a hospital. Acta radiol. (1966) Suppl. No. 254 p. 100.
- BOLLENGER R. R., COLARD J. F. et HENRY J. Compteur humain total du CFN à MoI étalonnage et observations sur 1500 mesures. In: Whole body counting p. 309 IAEA Vienna 1967.
- DEVELL L., VANNER L. and MANDAHIL B. Monitoring for internal contamination of nuclear energy personnel. Acta radiol. (1966) Suppl. No. 254 p. 111.
- DIRECTORY OF WHOLE BODY RADIOACTIVITY MONITORS (Monitor SN 31) IAEA Vienna 1964.
- EANS R. D. Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity. Annual Progress Report (MIT 952.2) (May 1965).

- LILLEGRAVEN A L and RUNDO J. Systematic arc calibration method for body radioactivity measurement *Acta radiol Ther Phys Biol* 3 (1965) 369
- Mc NEILL K G and MOHINDRA U K. Shapes of scintillation spectra *In* Assessment of radioactivity in man Vol I, p 67 IAEA, Vienna 1964
- MUTH H and OBERHAUSEN E. Physical measurements and clinical findings of persons with radium burdens *In* Assessment of radioactivity in man Vol II p 211 IAEA Vienna 1964
- PSZONA S, ADAMSKA B and ZARNOWIECKI K. Whole body counter for internal contamination control *Nukleonika* 8 (1963), 565
- STEINER A F. Radioisotopes in the skeleton naturally occurring radioisotopes in man *In* Radioisotopes in the biosphere, p 366 University of Minnesota Minneapolis 1960
- VENNART J, MAYCOCK G, GODFREY II E and DAVIES B L. Measurements of radium in radium luminizers *In* Assessment of radioactivity in man Vol II, p 277 IAEA Vienna 1964
- WENGER P and MILLER C E. Recherches sur l'accumulation et la toxicité du radium et du radiostrontium dans le corps humain *Helv chim Acta* 46 (1963) 467
- BENGTTSSON L G, DUDLEY R A et coll. Whole body counting of persons containing ^{90}Sr and ^{226}Ra an interlaboratory comparison *Helv Phys* 14 (1968) 209

Books received

We acknowledge with thanks under this heading books received for review we trust this will be regarded as a sufficient mark of appreciation of the courtesy of the sender. Reviews of selected items will appear as soon as an opportunity affords.

- BERG E, JANKOVICS R and BRASCH Z. Malignant tumours of the thyroid gland. Akadémiai Kiadó Budapest 1967.
- BREIT A. Angiographie der Uterustumoren und ihrer Residive. Georg Thieme Verlag Stuttgart 1967.
- COCCHI U and THURN P. Einführung in die Röntgendiagnostik. Georg Thieme Verlag Stuttgart 1967.
- DESOREZ A et PAPANICOLAOU N. La sémiologie scintigraphique du foie. Atlas pratique. Masson & Cie Paris 1967.
- DEUTSCHER RÖNTGENKONGRESS 1966. Georg Thieme Verlag Stuttgart 1967.
- DÜLLMANN W. Röntgendiagnostik der HWSakralfelenke und ihrer nahen Umgebung. Georg Thieme Verlag Stuttgart 1967.
- DONIZETTI P. Shadow and substance. The story of medical radiology. Pergamon Press Oxford 1967.
- DUX A. Koronarographie — Methodik, Indikation und Ergebnisse. Georg Thieme Verlag Stuttgart 1967.
- EDERKEN J and HODGES P J. Roentgen diagnosis of diseases of bone. Williams & Wilkins Baltimore 1967.
- FOCIEM H. Einführung in die geburtshilfliche und gynäkologische Röntgendiagnostik. Georg Thieme Verlag Stuttgart 1967.
- HARPER R A. Radiology of the duodenum. Lloyd Luke London 1967.
- HOWARD N. Mediastinal obstruction in lung cancer. Livingstone Edinburgh 1967.
- INSTRUMENTATION IN NUCLEAR MEDICINE. Volume 1. Edited by G J Hine. Academic Press New York 1967.
- JOHN D H O. Radiographic processing in medicine and industry. Focal Press London 1967.
- FOHLER A and ZIMMER H A. Grenzen des Normalen und Anfänge des Pathologischen im Röntgenbild des Skelets. Georg Thieme Verlag Stuttgart 1967.
- LACROIX L. Diagnostica pneumoradiografica in medicina interna. II. Pensiero Scientifico Roma 1967.
- LALLI A F. Essentials of urography. Charles C Thomas Springfield Illinois 1967.
- LOMBARDI G. Radiology in neuro-ophthalmology. Williams & Wilkins Baltimore 1967.
- ✓ PROGRESS IN PEDIATRIC RADIOLOGY. Volume 1. Edited by H J Kaufmann. S Karger Basel 1967.
- PROGRESS IN RADIOLOGY. Symposia and invited papers of the XIth International Congress of Radiology. Rome 22—28 September 1965. Edited by L Turano, A Ratti and C Biagini. Excerpta Medica Foundation Amsterdam 1967.
- ROGERS A W. Techniques of autoradiography. Elsevier Publishing Co Amsterdam 1967.

- LILLEGRAVEN A. L. and RUNDO J. Systematic arc calibration method for body radioactivity measurement *Acta radiol Ther Phys Biol* 3 (1965) 369
- Mc NEILL K. G. and MOHINDRA U. K. Shapes of scintillation spectra *In* Assessment of radioactivity in man Vol I, p 67 IAEA Vienna 1964
- MUTH H. and OBERHAUSEN E. Physical measurements and clinical findings of persons with radium burdens *In* Assessment of radioactivity in man Vol II, p 211 IAEA Vienna 1964
- PSZONA S. ADAMSKA B. and ZARNOWIECKI K. Whole body counter for internal contamination control *Nukleonika* 8 (1963), 565
- STTHNEY A. F. Radioisotopes in the skeleton naturally occurring radioisotopes in man *In* Radioisotopes in the biosphere p 366 University of Minnesota Minneapolis 1960
- VEYNNART J. MAYCOCK G. GODFREY H. E. and DAVIES B. L. Measurements of radium in radium luminizers *In* Assessment of radioactivity in man Vol II, p 277 IAEA Vienna 1964
- WENCER P. and MILLER C. E. Recherches sur l'accumulation et la toxicité du radium et du radiostrontium dans le corps humain *Helv. chim. Acta* 46 (1963) 467
- BENGTTSSON L. G. DUDLEY R. A. et coll. Whole body counting of persons containing ^{90}Sr and ^{226}Ra an interlaboratory comparison *Helv. Phys.* 14 (1968) 209

CYTOPLASMIC ULTRAVIOLET EXTINCTION OF STRONTIUM 90 INDUCED FIBROBLASTIC OSTEOSARCOMAS CORRELATED TO HISTOLOGIC APPEARANCE AND ULTRASTRUCTURE

by

PAR SUNDELIN and AGNAR NILSSON

The development of ^{90}Sr induced fibroblastic osteosarcomas through different morphologic stages of oncogenesis and the histologic appearance of overt tumours have been well established in mice (NILSSON 1962 NILSSON & ULLBERG 1962). The present study is concerned with the general histology of ^{90}Sr induced tumours and the question whether they follow the general tumour pattern, with correlation between cytoplasmic RNA active cell proliferation and the histologic and clinical signs of malignancy (AMBS & THORELL 1959 CASPERSSON & SANTENSON 1942 MOBERGER 1954 MOBERGER et coll 1952 THORELL 1947). This has been investigated histologically by ultraviolet cytophotometry and by electron microscopy of ^{90}Sr induced tumours.

Material and Methods

Male CBA mice 75 days old were injected intraperitoneally with ^{90}Sr corresponding to 0.7 to 0.8 $\mu\text{Ci/g}$ bodyweight. The mice weighed between 22 and

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- RUBIN A. Ileus und ileusartige Zustände im frühen Kindesalter. Georg Thieme Verlag Stuttgart 1967
- LAJTHY J., SZIKLA G., JOURNOUX P. et coll. Atlas d'anatomie stéréotaxique du télencéphale. Étude anatomo-radiologique. Masson & Cie, Paris 1967
- FER POGOSSIAN M. M. The physical aspects of diagnostic radiology. Hoeber Medical Division Harper & Row Publishers New York Evanston and London 1967
- TURANO L. Trattato di radiodiagnostica. Volume 2. Tomo 2. Fegato e vie biliari vie pancreatiche apparato urogenitale pneumoperitoneo addome acuto. Unione Tipografico Editrice Torinese Torino 1967
- TRITIUM LABELED MOLECULES IN BIOLOGY AND MEDICINE Edited by L. E. Reinendegen Academic Press New York and London 1967
- WAUBKE T. N. Fernseh Röntgen intraokularer Fremdkörper. Ferdinand Enke Verlag Stuttgart 1967
- (III) YEAR BOOK OF NUCLEAR MEDICINE Volume 2 Edited by J. L. Quinn Year Book Medical Publishers Chicago 1967
- LESBOK Z. B. Einführung in die Methodik der Röntgenuntersuchungen. Georg Thieme Verlag Stuttgart 1967

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- RUBIN A Ileus und ileusartige Zustände im frühen Kindesalter Georg Thieme Verlag Stuttgart 1967
- LAIRACI J SZIKLA G TOURNOUX P et coll Atlas d'anatomie stéréotaxique du télencéphale Etude anatomo radiologique Masson & Cie Paris 1967
- FERROGOSIAN M M The physical aspects of diagnostic radiology Hoeber Medical Division Harper & Row Publishers New York Evanston and London 1967
- TURANO L Trattato di radiodiagnostica Volume 2 Tomo 2 Fegato e vie biliari vie pancreatiche apparato urogenitale, pneumoperitoneo addome acuto Unione Tipografico-Editrice Torinese Torino 1967
- TRITIUM LABELED MOLECULES IN BIOLOGY AND MEDICINE Edited by L E Feinendegen Academic Press New York and London 1967
- WAUBKE T N Fernseh Röntgen intraokularer Fremdkörper Ferdinand Enke Verlag Stuttgart 1967
- (IHF) YEAR BOOK OF NUCLEAR MEDICINE Volume 2 Edited by J L Quinn Year Book Medical Publishers Chicago 1967
- ZIEBON Z B Einführung in die Methodik der Röntgenuntersuchungen Georg Thieme Verlag Stuttgart 1967

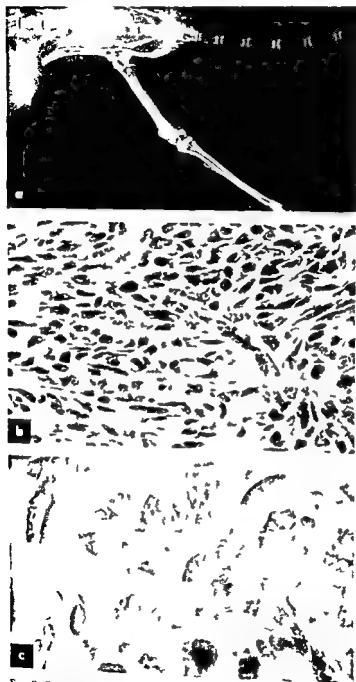


FIG 2 Group 4 Intramedullary tumour in right femur 769 days after administration of ^{90}Sr a) Ro ntgenogram b) van Gieson $\times 500$ c) Ultraviolet $\times 1000$

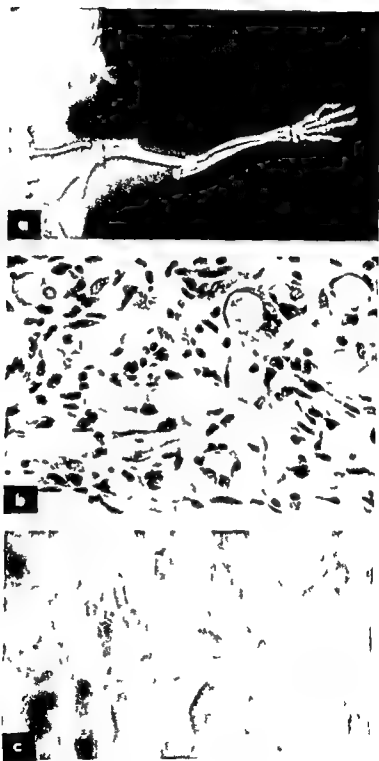


Fig 1 Group 3 Tumour from left humerus 276 days after ^{90}Sr injection. Proliferation of reticular cells and pleomorphism a) Roentgenogram b) van Gieson $\times 500$ c) Ultra violet $\times 1000$

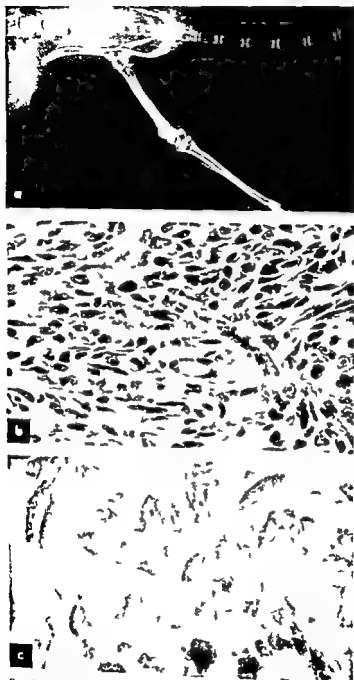


Fig 2 Group 4 Intramedullary tumour in right femur 269 days after administration of ^{90}Sr a) Roentgenogram b) van Gieson $\times 500$ c) Ultra violet $\times 1000$

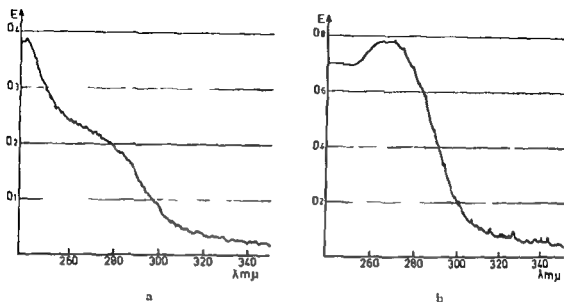


Fig 3 Ultraviolet extinction spectrum of cytoplasm a) Reticular cell with normal structure b) Tumour cell group 4 A specific nucleic acid absorption peak is visible

23 grams initially and were fed and kept under constant conditions before being killed at intervals between 190 and 377 days after the ^{90}Sr injection

For the histologic study, bone tissue were fixed in 5 % neutral formalin for 6 hours rinsed in tap water for 24 hours and decalcified under vacuum in 20 % formic acid for 3 hours, dehydrated, embedded in paraffin and sectioned at $5\ \mu$. All sections were stained by van Gieson's method

All the tumours used for this study were predominantly fibroblastic osteosarcomas with scanty osteoblastic elements and little osteoid formation. The ultraviolet analysis was performed on cells with evident fibroblastic character

The material could be classified by the microscopic appearance of the reticular cells in the bone marrow into nine stages of tumour development. Group 0 represented hypoplastic bone marrow with morphologically normal reticular cells and group 1 aplastic bone marrow with swelling and increased number of reticular cells. In group 2 there was a distinct proliferation of reticular cells but the tissue had the histologic appearance of fibrosis without neoplastic character. Group 3 (Fig 1), group 4 (Fig 2) and group 5 represented tumours situated completely within the bone marrow. The different groups were distinguished by the size of the tumour, cellularity and pleomorphism. Groups 6 to 8 consisted of tumours infiltrating and breaking through the compact bone and infiltrating the sur-

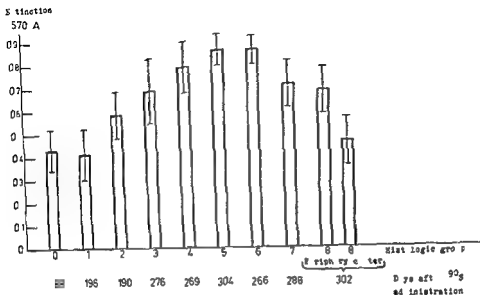


Fig 4 Cytoplasmic extinction in cells from increasingly more advanced tumours (see text). Each column represents mean value for 20 cells and standard deviation.

rounding soft tissue. The main differences between groups 6, 7 and 8 were successively increasing cellularity and size.

The femurs collected for electron microscopy belonged to the histologic groups 0, 2, 5 and 8. The material was fixed in OsO_4 , embedded in epon and sectioned with an LKB ultratome with a glass knife stained with lead citrate and examined in a Siemens Elmiskop IA.

For the ultraviolet microphotometry paraffin sections 3 μ thick were deparaffinized in chloroform, placed on quartz slides, immersed in glycerol for 2 days and mounted in glycerol. Cytoplasmic areas of fibroblastic cells were analysed in a UV spectrophotometer (CHANCE et coll 1959) by recording continuous spectra from 240 to 350 $m\mu$. The instrument was used in the present investigation with a Zeiss UV achromat condensor stopped down to NA 0.4 and ultrafluor objective NA 0.85. In the cytoplasm of tumour cells a specific absorption peak could generally be registered close to 260 $m\mu$. In apparently normal fibroblasts this peak was lower or could not be detected at all (Fig 3).

An estimate of the RNA contribution to the absorption at 260 $m\mu$ was obtained by recording the absorption before and after digestion and extraction of the RNA. Digestion was done with 1% RNase at 37°C for 60 minutes and

Table

Percentage reduction of cytoplasmic extinction values of group 5 tumour cells after digestion with RNase and extraction with perchloric acid T₁₀₀₀

Before digestion	After digestion	Percentage reduction
0.75	0.56	29
0.76	0.42	45
0.76	0.40	47
0.76	0.47	39
0.61	0.33	48
0.23	0.12	48
0.70	0.41	41
0.48	0.23	52
0.16	0.22	48
0.43	0.31	28
0.38	0.22	42
0.60	0.30	50
0.43	0.32	26
0.57	0.42	26
0.30	0.37	36
0.81	0.46	43
0.40	0.24	40
0.49	0.36	26
0.51	0.31	31
0.57	0.33	42
0.85	0.43	51
0.33	0.30	43
0.41	0.25	39
0.50	0.27	46
0.48	0.28	41

Mean \pm SD 40 \pm 8

extraction with 1 % perchloric acid at 4° C for 20 minutes followed by rinsing in water for 2 hours (PERRY et coll 1961). Identical points in the cytoplasmic areas were measured according to THORFLI (1947) before and after digestion and extraction in phosphatic buffer saline pH 7.2

Results and Discussion

The tumours will be considered here solely in relation to their histologic appearance and not in relation to their induction time since these are not necessarily correlated with each other.



Fig 5 Group 8 Tumour cell with abundant rough endoplasmic reticulum and aggregation of ribosome $\times 54\,000$

Digestion with RNase indicated that about 40 % of the cytoplasmic ultra violet extinction values were attributable to RNA (see Table). The values could clearly be correlated to the histologic groups (Fig 4). The morphologically more advanced stages of intramedullary tumour development were associated with increasing extinction values. The extramedullary tumour cells however had lower extinction values than the peak values obtained for intramedullary tumours. In overt tumours the cells towards the periphery also contained apparently greater amounts of cytoplasmic RNA than those in the center (cf CASPERSSON & SANTESSON 1942).

The cytoplasmic ultraviolet extinction reflects both ribosomal and soluble RNA. The ribosomal fraction can be further analysed with the ultrastructural technique.

The electron micrographs revealed no significant differences between normal reticular cells and group 2 tumour cells while the established tumour cells had some significant alterations.

The ribosomes were generally much more abundant in cells from established

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0.76	0.40	47
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0.64	0.33	48
0.23	0.12	48
0.70	0.41	44
0.48	0.23	52
0.16	0.22	48
0.43	0.31	28
0.38	0.22	42
0.60	0.30	50
0.43	0.32	26
0.57	0.42	26
0.58	0.37	36
0.84	0.46	45
0.40	0.24	40
0.49	0.36	26
0.51	0.35	31
0.57	0.33	42
0.85	0.43	51
0.53	0.30	43
0.41	0.25	39
0.50	0.27	46
0.48	0.28	41

Mean \pm SD 40 \pm 8

extraction with 1% perchloric acid at 4° C for 20 minutes followed by rinsing in water for 2 hours (PERRA *et coll* 1961). Identical points in the cytoplasmic areas were measured according to THORELL (1947) before and after digestion and extraction in phosphatic buffer saline pH 7.2

Results and Discussion

The tumours will be considered here solely in relation to their histologic appearance and not in relation to their induction time since these are not necessarily correlated with each other.

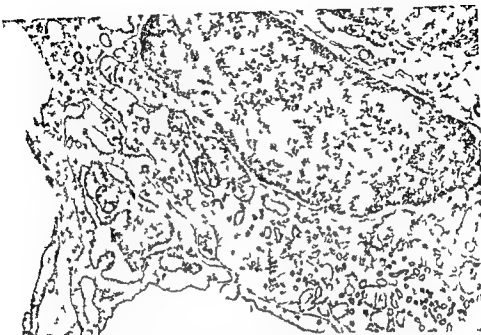


Fig 7 Group 0 Reticular cells with scanty electron dense material in the nucleus scant endoplasmic reticulum and few aggregations of free ribosomes $\times 74\,000$

changed. In some of the cells from the central parts of the group 8 tumours however the number of mitochondria was markedly decreased.

The nuclei of tumour cells were often lobulated and contained electron dense material with over all spread in the nucleus (Figs 5 and 6) while the normal reticular cells had scanty dense material concentrated along the nuclear membrane (Fig 7).

The abundance of endoplasmic reticulum seems to vary considerably in different kinds of tumour cells. In many carcinomas investigated the ergastoplasm has been found to be scanty and the majority of the ribosomes are free. In other types of tumours — Rous sarcomas, osteosarcomas, myelomas and pituitary adenomas — the amount of ergastoplasm has been reported to be increased in comparison with the corresponding normal cells (EPSTEIN 1957, PEACH *et coll* 1961). It is obvious that the cells with abundant ergastoplasm of the rough type have a very high UV extinction and it is possible that they are responsible for the formation of collagen which is present in large amounts in these tumours. Further investigations are in progress to elaborate on this point.



Fig 6 Group 5 Tumour cell with numerous mitochondria and sac like distension of endoplasmic reticulum (arrow) $\times 12\,000$

tumours, and in some of the tumour cells the endoplasmic reticulum was dense and almost exclusively of the rough type (Fig 5). In other cells it was scanty, and the ribosomes were mostly free. Small aggregations of ribosomes were found in reticular cells of group 0 and 2 but they were larger and more numerous in cells of established tumours, especially in those with a scanty endoplasmic reticulum. In some of the group 8 tumour cells there were few free and bound ribosomes, in these cells, other cytoplasmic organelles were also poorly developed, and they seemed to correspond to the centrally situated cells with low UV extinction values. The endoplasmic reticulum of tumour cells characteristically had sac like distensions filled with electron dense material (Fig 6). Such distensions have been described in strontium induced fibroblastic osteosarcomas and other tumours (Nilsson 1962) but also in non tumourous inflammatory tissue (Peach et al 1961), and it has been demonstrated by Goldberg & Green (1964) that they are the site for collagen formation.

The size and shape of the mitochondria were irregular both in tumourous and non tumourous reticular cells but the internal mitochondrial architecture was un-

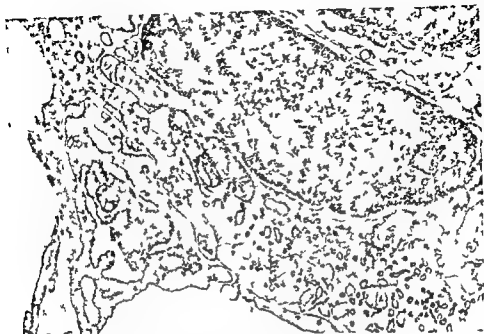


Fig 7 Group II Reticular cells with scanty electron dense material in the nucleus; scanty endoplasmic reticulum and few aggregation of free ribosomes $\times 24,000$

changed. In some of the cells from the central parts of the group II tumours, however, the number of mitochondria was markedly decreased.

The nuclei of tumour cells were often lobulated and contained electron dense material with over all spread in the nucleus (Figs 5 and 6) while the normal reticular cells had scanty dense material concentrated along the nuclear membrane (Fig 7).

The abundance of endoplasmic reticulum seems to vary considerably in different kinds of tumour cells. In many carcinomas investigated the ergastoplasm has been found to be scanty and the majority of the ribosomes are free. In other types of tumours — Rous sarcomas, osteosarcomas, myelomas and pituitary adenomas — the amount of ergastoplasm has been reported to be increased in comparison with the corresponding normal cells (Epstein 1957; Peach et al 1961). It is obvious that the cells with abundant ergastoplasm of the rough type have a very high UV extinction and it is possible that they are responsible for the formation of collagen which is present in large amounts in these tumours. Further investigations are in progress to elaborate on this point.

SUMMARY

^{90}Sr induced osteosarcomas in different stages of development were investigated by means of ultraviolet microphotometry and electron microscopy. Successively increasing UV extinction values could be correlated to morphologically more advanced stages of tumour development.

ZUSAMMENFASSUNG

Osteosarkome in verschiedenen Entwicklungsstadien, die durch Strontium 90 verursacht waren, wurden mittels der ultravioletten Mikrophotometrie und Elektronenmikroskopie untersucht. Successiv zunehmende UV Auslöschungswerte konnten mit morphologisch fortgeschrittenen Stadien der Tumorentwicklung korreliert werden.

RÉSUMÉ

Des ostéosarcomes induits par le ^{90}Sr à différents stades de développement ont été examinés par microphotométrie en ultra violet et par microscopie électronique. On a pu établir une corrélation entre les valeurs croissantes d'extinction du cytoplasme en ultra violet et les stades d'avancement morphologique du développement des tumeurs.

REFERENCES

- AMNS E. and THORELL B. Die Cyto-genese bei der Virus leukämia des Huhnes. *Acta haemat* 21 (1959) 284
- CASPERSSON T. and SANTESSON L. Studies on protein metabolism in the cells of epithelial tumours. *Acta radiol* (1942) Suppl. No. 46
- CHANCE B. PERRY R. THORELL B. and ÅKERMAN L. Highly sensitive recording microspectrophotometer. *Rev. Sci. Instrum.* 36 (1969) 735
- FESTIN M. A. The fine structural organisation of Rous tumour cells. *J. biophys. biochem. Cytol.* 3 (1957) 851
- GOLDBERG B. and GREEN H. An analysis of collagen secretion by established mouse fibroblast lines. *J. Cell Biol.* 22 (1964) 227
- MOBERGER G. Malignant transformation of squamous epithelium. *Acta radiol* (1954) Suppl. No. 112
- RINGERTZ N. and HÅKANSSON E. Study in nucleic acid metabolism in gliomas. *Acta Univ. int. Cancer* 8 (1952) 591
- NILSSON A. ^{90}Sr induced osteosarcomas. *Acta vet. scand.* 3 (1962) 122
- Histogenesis of ^{90}Sr induced osteosarcomas. *Acta vet. scand.* 3 (1962) 185
- and ULLBERG S. Uptake and retention of strontium 90 in mouse tissues studied by whole animal autoradiography and impulse counting. I. *Acta radiol.* 58 (1962) 81
- — Uptake and retention of strontium 90 in strontium 90 induced osteosarcomas. II. *Acta radiol.* 58 (1962) 168
- PEACH R. WILLIAMS G. and CHAPMAN J. A. A light electron optical study of regenerating tendon. *Amer. J. Path.* 38 (1961) 495
- PERRY R. P. ERRERA M. and HELL A. Kinetics of nucleic acid incorporation into nuclear and cytoplasmic RNA. *J. biophys. biochem. Cytol.* 11 (1961) 1
- THORELL B. Studies on the formation of cellular substances during blood cell production. Henry Kimpton London 1947

TOPICAL TREATMENT OF ULCERATIVE MAMMARY CARCINOMA BY THIOTEPA COMPRESSES

by

A P ANDERSEN H BRINCKER and A SELL

The alkylating cytostatic thiotepa (N N N triethylene thiophosphoramidate) has been used since 1953 for the palliative treatment of a large number of malignant diseases. It has usually been administered parenterally but topical application has also been tried successfully in certain benign and malignant conditions. The intrapleural and intraperitoneal instillation of thiotepa performed once to several times in single doses of 10 to 65 mg has proved effective in the treatment of recurrent malignant effusions. BATEMAN *et al* (1955) for instance reported good effects in eleven out of sixteen patients with pleural effusion and in five out of eight patients with peritoneal effusion. GROESBECK & CROMORE (1962) found the same favourable effect in thirteen out of fifteen patients with pleural effusion and in seven out of twelve with peritoneal effusion.

A number of widespread benign and malignant bladder papillomas have been successfully treated by intravesical instillations of thiotepa. The doses have generally been 30 to 60 mg repeated four to six times at intervals of 2 to 7 days. The effect has been most marked upon superficial papillomatous tumours while infiltrating tumours have failed to respond. JONES (1963) for

Submitted for publication 11 December 1967

SUMMARY

^{90}Sr induced osteosarcomas in different stages of development were investigated by means of ultraviolet microphotometry and electron microscopy. Successively increasing UV extinction values could be correlated to morphologically more advanced stages of tumour development.

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Osteosarkome in verschiedenen Entwicklungsstadien die durch Strontium 90 verursacht waren wurden mittels der ultravioletten Mikrophotometrie und Elektronenmikroskopie untersucht. Successiv zunehmende UV Auslöschungswerte konnten mit morphologisch fortgeschrittenen Stadien der Tumorentwicklung korreliert werden.

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Des ostéosarcomes induits par le ^{90}Sr à différents stades de développement ont été examinés par microphotométrie en ultra violet et par microscopie électronique. On a pu établir une corrélation entre les valeurs croissantes d'extinction du cytoplasme en ultra violet et les stades d'avancement morphologique du développement des tumeurs.

REFERENCES

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- PERRY R. P. ERRERA M. and HELL A. Kinetics of nucleic acid incorporation into nuclear and cytoplasmic RNA. *J. biophys. biochem. Cytol.* 11 (1961) 1.
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Table

Results of treatment with thiotepe in 11 patients with ulcerating breast cancer during the period October 1964 to August 1966

Case	Age	Lesion	Applications/ days	Total dose thiotepe mg	Additional treatment
1	64	Adenocarcinoma	25/33	375 mg	Prednisone
2	63	Carcinoma	15/2	225 mg	Stilboestrol + prednisone
3	56	Sci scirr carcinoma	23/23	345 mg	Hypophysectomy 3 months/earlier
4	72	Sci carcinoma	28/28	120 mg	None
5	47	Intracanal carcinoma	19/19	285 mg	Prednisone
6	59	Sciirr carcinoma	13/13	185 mg	Testosterone
7	75	Sci sciirr carcinoma	21/21	915 mg	Prednisone
8	56	Carcinoma	22/40	330 mg	Prednisone
9	64	Sciirr carcinoma	12/19	180 mg	Prednisone
10	61	Carcinoma	82/122	1 230 mg	Stilboestrol
11	51	Sci sciirr carcinoma	14/16	210 mg	Prednisone

* Symbols — no effect + sporadic epithelialization ++ 50 per cent epithelialization +++ total epithelialization

instance, reported total or almost total disappearance of multiple papillomatous tumours in seventeen out of twenty four patients. Esquivel et coll (1965) recorded complete tumour destruction in three, and partial destruction in two out of eight patients with benign papillomatosis. Two of a group of twelve patients with carcinomatous lesions responded only slightly the tumours were quite superficial (stage A) in both. In all the other patients with more deeply infiltrating tumours the treatment was ineffective.

CHENG & VEENEMA (1965) applied thiotepe topically in six patients with

Table (cont.)

Min. values/ Leucocytes (L) Platelets (P)	Effect	Survival after treatment months	Comments
No depression	+++	6	(See Fig. 1)
No haematological control	+++	13	(See Fig. 2)
No depression	++	9	Recurrent ulceration 6 months later New topical thiotepa without effect
No depression	++	4	
L 2100 P no depression	++	17	Additional intrapleural thiotepa (40 mg)
No depression	++	2	
L 100 P 10 000	+		(See Fig. 3)
No depression	+	14	
No depression	—	8	
L 1100 P 12 000	++	8	Ulcerating primary tumour
No depression	+	5	Pyococcus infection during thiotepa treatment

penile tumours. In dealing with tumours of the urethra they used suppositories of 15 mg applied once daily for 2 hours while tumours affecting the glans penis were bathed in a solution of 60 mg thiotepa in 60 ml distilled water once or twice daily for 2 hours at a time. Out of four patients with condylomata acuminata they obtained complete disappearance of the lesion in one patient in whom the lesion affected the urethra and partial disappearance in three patients in whom the lesions affected the glans. Superficial regression of the tumours was achieved in only two patients with squamous cell carcinoma.

Table

Results of treatment with thiotepea in 11 patients with ulcerating breast cancer during the period October 1964 to August 1966

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3	56	Sol scirr. carcinoma	23/23	345 mg	Hypophysectomy 9 months/earlier
4	72	Sol carcinoma	28/28	420 mg	None
5	47	Intracanal carcinoma	19/19	285 mg	Prednisone
6	59	Scirr. carcinoma	13/13	185 mg	Testosterone
7	75	Sol scirr. carcinoma	21/21	315 mg	Prednisone
8	56	Carcinoma	22/40	330 mg	Prednisone
9	64	Scirr. carcinoma	12/19	180 mg	Prednisone
10	61	Carcinoma	87/122	1 230 mg	Stilboestrol
11	51	Sol scirr. carcinoma	14/16	210 mg	Prednisone

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Fig 1 Case 1 a) Ulceration in the metastatic scar b) Total epithelialization 33 days later after 25 applications of thioteпа

ulcerated area while in five patients the epithelialization covered more than 50% of the area. Three patients had scattered epithelialization while the treatment failed in one patient who will be discussed later.

Illustrative cases

Case 1 Woman aged 64 underwent right side mastectomy with axillary dissection in March 1961. The microscopic examination disclosed adenocarcinoma. Postoperative irradiation by the McWhirther field technique was given.

Progressive cutaneous metastases around the mastectomy scar were present in November 1963. In March 1964 there were diffuse neoplastic infiltrations in the entire left breast and left side axillary metastases. Simple palliative left mastectomy was then performed and in April treatment with androgenic hormones was started. The skin metastases regressed slightly. In September 1964 carcinoma of the right pleural cavity was treated by pleural puncture and instillation of ^{198}Au .

Regression of the cutaneous metastases was noted in February 1965 and an area of ulceration 5 cm \times 7 cm appeared in the right mastectomy scar (Fig 1a). The androgenic therapy was discontinued and prednisone was instituted. At the same time the ulceration was treated with thioteпа compoesses (25 applications/33 days with a total of 375 mg thioteпа). This resulted in total epithelialization of the area (Fig 1b) while other non-ulcerating cutaneous lesions progressed.

In September 1965 there were signs of hepatic metastases and death occurred at the end of the month.

A few patients with *mycosis fungoides* have been treated by thiotepra 0.2 % in a linolin petroleum jelly base and were much improved (GRUPPER & SIKKIS 1965, MICHIEL et coll 1965).

The recurrence rate of pterygium, reported to be 20 % to 30 % after surgery alone, may be greatly reduced by the postoperative instillation into the conjunctiva of thiotepra 0.05 % in Ringer's solution every third hour for 6 to 8 weeks. This treatment is said to produce no local irritation. CASADY (1966) has reported the results of treating 78 patients, among whom there were six recurrences, out of this series, however, forty six had been treated for more than 2 months and in these there were no recurrences.

VOUTILAINEN & SALMI (1965) have published two cases of ulcerating cutaneous metastases from mammary carcinoma treated with compresses soaked in thiotepra solution. In one of these cases they used a solution of 15 mg thiotepra applied once daily, with a total of 20 applications in the course of 36 days. Colimycin compresses were used in the intervals between the applications. Three months after the discontinuation of the treatment the ulceration had undergone epithelialization. In the other case, they employed a solution of 30 mg thiotepra, applied 8 times in the course of 21 days. One month after the treatment had been discontinued the ulceration had diminished but thereafter it again progressed.

We have tested the last mentioned method, which is easy to administer and has produced good palliation in several cases.

Method. An amount of 15 mg thiotepra is dissolved in 20 to 30 ml sterile water. A compress of the same size as the ulceration is soaked in the solution, applied to the ulcerated site, covered with gutta percha, and held by an ordinary dressing. The compresses are changed daily. While the treatment is continued, white cell and platelet counts are made 2 to 3 times weekly. Should signs of bone marrow depression appear, the applications should be interrupted immediately and not be resumed until the marrow has been restored to normal.

Results

We have treated 11 patients with ulcerating breast cancer by the above procedure during the period October 1961 to August 1966. The results are given in the Table.

One patient (Case 10) had an ulcerating primary tumour, while the others had cutaneous metastases that had ulcerated. The material was not selected, except for the fact that only patients in an acceptable general condition were included. In two patients, the treatment resulted in total epithelialization of the



Fig. 3 Case 7 Widespread ulceration of the metastatic areas on the anterior aspect of the right chest and right upper arm

given but again had no effect upon the necrosis. Electron therapy (10 McV 3 150 rad/31 days) also seemed ineffective. Distant metastases gradually appeared and the patient died in November 1966.

Discussion

Alkylating agents are chemically very active substances whose cytotoxic effect presumably consists mainly in an inhibition of the DNA synthesis. Morphologically the effect is apparent as an inhibition of mitotic activity with characteristic chromosomal breakages. The cytotoxic action is not selective and therefore the concentration in the tumour should preferably be higher than in the surrounding tissue. This is obtained by topical application of the agent.

The treatment with thiotepea compresses failed entirely in one of the patients in the present series (Case 9). The characteristics of this case was ulceration covered with thick encrustations, which is possibly the explanation of the absence of any effect from the thiotepea.

Ten of the eleven patients received hormone medication at the same time as the thiotepea application. The cases were analysed with a view to assessing to what extent the hormone may have contributed to the effect. In two instances (Cases 1 and 10) the hormone medication was started almost simultaneously with the thiotepea applications which makes the evaluation difficult but in these two cases other metastatic lesions progressed in spite of



Fig. 2 Case 2 a) Ulceration of widespread cutaneous metastases b) Total epithelialization after 15 applications of thiotepea

Case 7 Woman, aged 75 had right side mastectomy in March 1963. Microscopy showed scirrhous carcinoma. No postoperative radiotherapy.

In September 1964 increasing number of cutaneous metastases in the right chest and right upper arm. prednisone medication was ineffective.

In February 1965 there was also widespread ulceration in the metastatic areas on the anterior aspect of the right chest and right upper arm (Fig. 3). Treatment with thiotepea compresses was instituted (21 applications/21 days with a total of 915 mg thiotepea). Epithelialization began to appear along the margins and central islets of epithelium were observed but at the same time the absorption of thiotepea from the ulcerated surfaces severely depressed the bone marrow. There was a fall in the white blood count to $100/\mu\text{l}$ and of the platelets to $10\,000/\mu\text{l}$. In spite of prednisone in large doses the bone marrow could not be restored and the patient died of profuse rectal bleeding due to severe thrombocytopenia a month later.

Case 9 Woman, aged 64 who in February 1962 had ulcerating carcinoma of the left breast. Preoperative radiotherapy was followed by right mastectomy in April 1962. Microscopy showed diffuse scirrhous carcinoma. Postoperative irradiation of the regional lymph nodes and roentgen castration.

In November 1964 there were cutaneous metastases on the anterior surface of the right chest, with ulceration $2\text{ cm} \times 2\text{ cm}$ in size which yielded to local irradiation.

In August 1965 further progression of lesion with ulceration despite prednisone therapy. The lesion measured $12\text{ cm} \times 18\text{ cm}$ in February 1966 there was a $7\text{ cm} \times 7\text{ cm}$ large central area of ulceration and marked necrosis. Treatment with thiotepea compresses was started (12 applications/19 days with a total of 180 mg thiotepea). The treatment had no effect either upon the ulcerations or upon the necrosis. Prolonged energetic antiseptic therapy topically was



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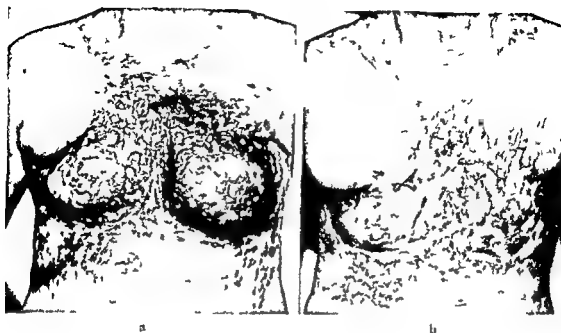


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In September 1964 increasing number of cutaneous metastases in the right chest and right upper arm. prednisone medication was ineffective.

In February 1965 there was also widespread ulceration in the metastatic areas on the anterior aspect of the right chest and right upper arm (Fig. 3). Treatment with thiotepea compresses was instituted (21 applications/21 days with a total of 945 mg thiotepea). Epithelialization began to appear along the margins and central islets of epithelium were observed, but at the same time the absorption of thiotepea from the ulcerated surfaces severely depressed the bone marrow. There was a fall in the white blood count to $100/\mu\text{l}$ and of the platelets to $10\,000/\mu\text{l}$. In spite of prednisone in large doses the bone marrow could not be restored and the patient died of profuse rectal bleeding due to severe thrombocytopenia a month later.

Case 9 Woman, aged 64, who in February 1962 had ulcerating carcinoma of the left breast. Preoperative radiotherapy was followed by right mastectomy in April 1962. Microscopy showed diffuse scirrhous carcinoma. Postoperative irradiation of the regional lymph nodes and roentgen castration.

In November 1964 there were cutaneous metastases on the anterior surface of the right chest with ulceration $2\text{ cm} \times 2\text{ cm}$ in size which yielded to local irradiation.

In August 1965 further progression of lesion with ulceration despite prednisone therapy. The lesion measured $12\text{ cm} \times 18\text{ cm}$ in February 1966 there was a $7\text{ cm} \times 7\text{ cm}$ large central area of ulceration and marked necrosis. Treatment with thiotepea compresses was started (12 applications/19 days with a total of 180 mg thiotepea). The treatment had no effect either upon the ulcerations or upon the necrosis. Prolonged energetic antiseptic therapy topically was



Fig. 3 Case 7 Widespread ulceration of the metastatic areas on the anterior aspect of the right chest and right upper arm

given but again had no effect upon the necrosis. Electron therapy (10 MeV 3150 rad/31 days) also seemed ineffective. Distant metastases gradually appeared and the patient died in November 1966.

Discussion

Alkylating agents are chemically very active substances whose cytotoxic effect presumably consists mainly in an inhibition of the DNA synthesis. Morphologically the effect is apparent as an inhibition of mitotic activity with characteristic chromosomal breakages. The cytotoxic action is not selective and therefore the concentration in the tumour should preferably be higher than in the surrounding tissue. This is obtained by topical application of the agent.

The treatment with thioteпа compresses failed entirely in one of the patients in the present series (Case 9). The characteristics of this case was ulceration covered with thick encrustations which is possibly the explanation of the absence of any effect from the thioteпа.

Ten of the eleven patients received hormone medication at the same time as the thioteпа application. The cases were analysed with a view to assessing to what extent the hormone may have contributed to the effect. In two instances (Cases 1 and 10) the hormone medication was started almost simultaneously with the thioteпа applications which makes the evaluation difficult but in these two cases other metastatic lesions progressed in spite of



Fig 2 Case 2 a) Ulceration of widespread cutaneous metastases b) Total epithelialization after 14 applications of thiotepea

Case 7 Woman aged 75 had right side mastectomy in March 1963. Microscopy showed scirrhous carcinoma. No postoperative radiotherapy.

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therapy, or who were simultaneously on parenteral chemotherapy CHENG & VEENEMA observed a slight depression of the white blood count in the topical treatment of penile and urethral tumours with thioteпа MICHEL *et coll* have reported a case of leukocyte and platelet depression after the topical treatment of mycosis fungoides with a total dose of 1.4 g thioteпа/34 days CASSADY noted no absorptive side effects in the treatment of pterygium and VOUTI LAINEN & SALMI observed no such effects in their two patients treated for ulcerative mammary carcinoma The present results indicate however that the blood picture should be carefully checked during the treatment which should be interrupted immediately if signs of bone marrow depression appear Furthermore it seems inadvisable to administer more than 15 mg thioteпа daily, and particular caution should be observed with large areas of ulceration and prolonged treatment

It does not seem reasonable to try this treatment unless the patients are in a fair general condition and are likely to survive for a certain length of time Incidentally the treatment is well suited for out patient use provided that the haematologic condition can be followed

SUMMARY

The results of the local application of thioteпа compresses to ulcerative mammary carcinoma in 11 patients are reported The risk of haematologic complications is stressed The literature on this topical treatment is reviewed

ZUSAMMENFASSUNG

Es wird über die Resultate der Behandlung mit lokalen Kompressen von Thioteпа von 11 Patienten mit ulcerativen Mammakarzinomen berichtet Das Risiko von hamatologischen Komplikationen wird betont Die Literatur wird besprochen

RÉSUMÉ

Les auteurs présentent les résultats de l'application locale de compresses imbibées de Thioteпа sur des cancers du sein ulcérés chez 11 malades Ils insistent sur le danger des complications hématologiques Ils donnent une revue de la littérature sur ce traitement local

REFERENCES

- BATEMAN J. C. MOLLTON B. and LARSEN A. J. Control of neoplastic effusion by phosphoramidate chemotherapy Arch intern Med 95 (1955) 713
CASSADY J. R. The inhibition of pterygium recurrence by Thioteпа Amer J Ophthal 61 (1966) 88f

the hormone. In the other eight patients the medication had been instituted several months before the thiotepe treatment without having favourably affected the ulcerating area, so that it is not likely that the hormone had any share in the effect.

VOUTILAINEN & SALMI recommend the use of colimycin compresses during the intervals between the thiotepe applications in order to prevent the growth of microorganisms in the treated area. This or similar procedures were not used in the present series. One of the patients (Case 11) developed a pyocyanus infection in the ulcerated area, while the others exhibited regression of superficial infectious lesions, in keeping with the fact that alkylating agents per se are bactericidal.

Three of the patients developed signs of bone marrow depression in the course of the treatment. This manifested itself as a decrease in the white cell or platelet count. In one of these patients (Case 5), however, it was difficult to assess the share in these complications of the thiotepe compresses as, due to a pleural effusion, intrapleural thiotepe therapy (45 mg) was administered at the same time. Case 10 developed a depression of the bone marrow after prolonged treatment (1 230 mg thiotepe/122 days) in spite of a rather small area of ulceration (about 13 square cm), the signs consisted of decreased white cell and platelet counts and progressing anaemia. In the course of a month blood transfusions restored the haematologic condition to normal, however. Case 7 had very widespread ulcerating lesions and was given a daily dose of 15 mg thiotepe (the usual is 15 mg). In the course of three weeks there was a massive decrease in the haemoglobin level, white cell and platelet counts, and the patient died of haemorrhagic diathesis.

Thiotepe, whose molecular weight is 189, can be absorbed to a certain extent from the outer and inner surfaces of the body, especially if these have undergone pathologic changes. Indeed, others have also reported absorptive side effects with thiotepe. ESQUIVEL *et coll.*, for instance, observed an action upon the bone marrow in five out of twenty patients treated by intravesical instillations of thiotepe, however, all rapidly improved. ORAVISTO (1965), treating six patients by intravesical thiotepe, found severe leukocytopenia and thrombocytopenia after a total dose of 150 mg thiotepe in one patient while another patient died of massive hepatic necrosis 16 days after 120 mg thiotepe/7 days, after having had but a modest decrease in the white cell and platelet counts. EDGREN *et coll.* (1966) have also published a case of severe bone marrow depression after 360 mg thiotepe/8 days in the urinary bladder.

GROESBECK & CUDMORE found a slight haematologic depression in a few patients treated with thiotepe, administered intrapleurally and intraperitoneally, although only in those who had already received radiotherapy, ¹⁹⁹Au

therapy or who were simultaneously on parenteral chemotherapy CHENG & VEENEMA observed a slight depression of the white blood count in the topical treatment of penile and urethral tumours with thioteпа MICHEL et coll have reported a case of leukocyte and platelet depression after the topical treatment of mycosis fungoides with a total dose of 1.4 g thioteпа/34 days CASSADY noted no absorptive side effects in the treatment of pterygium and VOUTI LAINEN & SALMI observed no such effects in their two patients treated for ulcerative mammary carcinoma The present results indicate however that the blood picture should be carefully checked during the treatment which should be interrupted immediately if signs of bone marrow depression appear Furthermore it seems inadvisable to administer more than 15 mg thioteпа daily and particular caution should be observed with large areas of ulceration and prolonged treatment

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- BATEMAN J C MOLLTON B and LARSEN A J Control of neoplastic effusion by phosphoramidate chemotherapy Arch intern Med 95 (1955) 713
CASSADY J R The inhibition of pterygium recurrence by Thioteпа Amer J Ophthal 61 (1966) 886

- CHENG S F and VEENEMA R J Topical application of Thio Tepa to penile and urethral tumors J Urol 91 (1965), 259
- EDGREN B FORSGREN L and BOSTROM H Grav benmargsskada efter blåsinstallationer med tiotépa (in Swedish) Nord Med 75 (1966) 481
- ESQUIVEL JR E L MACKENZIE A R and WHITMORE JR W F Treatment of bladder tumors by instillation of thio TEPA actinomycin D or 5-fluorouracil Invest Urol 2 (1965) 381
- GROESBECK H P and CUDMORE J T P Intracavitary Thio TEPA for malignant effusions Amer Surg 28 (1962) 90
- GRUPPER C et SIRAIS L Le thiotépa en applications locales avec occlusion dans le mycosis fongique Bull Soc franç Derm Syph 72 (1965), 338
- JONES H C The topical use of cytotoxic drugs for bladder cancer Proc roy Soc Med 56 (1963) 751
- MICHEL P J CRETIN J et LÉPINE Y Prémycosis rebelle au traitement classique Heureux résultat d'un essai de traitement local antimitotique (thiotépa) sous pansement occlusif Bull Soc franç Derm Syph 72 (1965) 27
- ORAVISTO K J Topical use of Thio Tepa for tumours of the bladder Urol int 20 (1965) 23
- VOUTILAINEN A and SALMI R Skin metastases of mammary cancer treated by Thio TEPA solution compresses Ann Chir Gynaec Fenn 54 (1965) 401

TREATMENT METHOD AND DOSE DISTRIBUTION IN RADIOTHERAPY OF CARCINOMA OF THE CERVIX

by

PER BERGSJØ and PER KRISTIANSEN

The basic principles of radiation treatment of carcinoma of the uterine cervix in our hospital have remained unchanged since 1932. With the exception of a report by GRANDE (1958) on the dosimetry of a special vaginal applicator, no detailed account of the system seem, however, to have been published. Our aim with the present paper is to present the whole procedure, including the dose distribution, as it has been practised up to now. The system will be referred to as the Oslo method.

Principles and techniques of the Oslo method. Radium is the standard primary treatment of all forms and stages of invasive cervical carcinoma. It is exhibited either as the only form of treatment or supplemented by surgery (early stages) or external radiation (more advanced stages). Detailed accounts of the various combinations of surgery and irradiation in early stages have been given by SCHJOTT RIVERS (1951), DAHLE (1959) and KOLLER (1964), and the interested reader is referred to these reports.

The radium treatment is a modification of the Paris method and consists of two applications: one intra uterine and one intravaginal. The intra uterine

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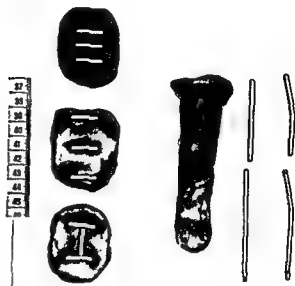


Fig 1 Intrauterine and vaginal applicators. A vaginal applicator is seen in the middle. The three configurations of vaginal radium are referred to as (from top to bottom) I, II and III in the text.

applicator carries 20 or 30 mg radium, depending on the length of the uterine cavity, and the intravaginal applicator bears 30 mg radium. The duration of each application is 120 hours (5 days) to produce a total of 6 000 or 7 200 mg hours of radium. As the two applicators may be employed either simultaneously or in succession, the same total dose may be given at two different dose rates.

The intra uterine applicators (Fig 1) are straight or slightly angulated cylinders, measuring 6 mm \times 80 mm (active length 68 mm) and 6 mm \times 58 mm (active length 44 mm) for 30 and 20 mg radium, respectively. The filter equals 1.5 mm Pt.

The vaginal radium is applied in 10 mg tubes of gold or platinum, with an active length of 13.5 mm, and a filter equal to 1 mm Pt. The three vaginal tubes are usually placed on the shallow, bell-shaped end of an applicator moulded by hand to fit the individual cervix and tumour from a dental impression compound (Kerr's plastic). The tubes are placed sagittally or in an H form, with 20 to 40 mm separating the lateral tubes. Also a pessary-shaped plastic applicator without shaft (GRANDT 1958) which is used in individual cases has the shape of an H. Three different configurations of vaginal radium applicators are given in Fig 1.

The external radiation was previous to 1958 administered with 170 kV roentgen rays (filter 1 mm Cu), 3 000 R at the skin, to two anterior and two posterior fields, each 10 cm \times 15 cm in size, delivered over approximately 40 days.

Betatron treatment has been the rule since 1958. All the patients received 31 MeV roentgen rays from a betatron until 1964, but since then a number of

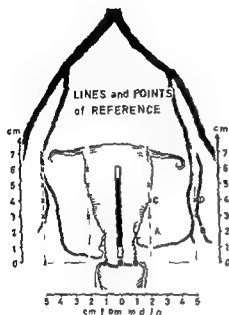


Fig 2 Lines and points of reference Of the three vaginal tubes r_1 lies closest to and r_3 farthest away from the side of reference

patients have been treated with 33 MeV roentgen rays from a new betatron the old betatron was utilized for the remainder

The 31 MeV machine has a circular pelvic field 20 cm in diameter (total 314 cm²), and each daily fraction is 200 rad. The total dose of a standard treatment for carcinoma of the cervix was 4 000 rad from 1958 to 1960 since then it has been 5 000 rad to the periphery (pelvic wall area) the central dose being kept at 4 000 rad with a central shield 7 cm in diameter. These doses refer to the absorption maximum located about 5 cm below the body surface. Half of the treatments are given from the front and half from the back.

The 33 MeV machine has a 16 cm \times 16 cm (256 cm²) pelvic field. A shield in the lower central part of the field was designed to produce doses equal to those of the 31 MeV apparatus. The daily fractions and total doses are as described above.

The daily fractions are given 3 to 6 times per week. An uninterrupted series of betatron treatment is spread over four to five weeks.

Measurement of dose distribution Some simple measurements have been performed in a special phantom to obtain knowledge of the dose distributions and an idea of the doses absorbed at certain points. The further aim of these measurements was to check the reliability of the calculated values which are based on

standard tables and isodose charts. Rectal dose measurements in a series of patients with radium applications have also been made.

Points of reference The anatomical points of interest are the tumour itself, the parametrium, and the lymphatic system. The rectal dose is of major importance regarding side effects. Based on these considerations certain lines and points of reference were defined, and a phantom was constructed according to these principles.

The points of reference lie along two straight lines parallel to the uterine canal 2 cm and 5 cm, respectively, lateral to it in the sagittal planes, for the sake of simplicity the uterine canal is considered as a straight line. The medially situated line corresponds to the median part of the parametrium, which is the tumour bearing area in cervical carcinoma stage II B. The lateral line is in the area of the pelvic wall, as shown in Fig. 2.

The commonly adopted points of reference, points A and B, are located on the lines of reference. As defined by TOD & MERFITH (1953), point A lies 2 cm lateral to the central canal of the uterus and 2 cm above the mucous membrane of the lateral fornix in the axis of the uterus, point B lies 3 cm lateral to point A at the same level. In addition to points A and B the doses at two other points, called C and D, have been calculated, these are located 2 cm above the former points on the median and lateral lines of reference, respectively, as shown in Fig. 2.

An accurate determination of the betatron contribution on the lines of reference is difficult because of individual variations. Considering that the treatments are generally given both from the front and the back, the 10 cm depth dose was thought to represent the average dose in the target area. The frontal plane 10 cm from the body surface was therefore chosen for reference.

Measurement of radium doses As previously explained the vaginal radium tubes are placed on the applicators to cover the individual tumour in the best possible way, which of course means individual differences in dose distribution. We have studied the doses delivered by the three different configurations I, II and III illustrated in Fig. 1. These are typical forms used to treat a wide range of cervical carcinomas of all forms and stages.

A perspex phantom (Fig. 3) was designed to accommodate the three vaginal radium tubes of configuration I and the straight uterine applicators. The design permitted several angles (30° , 60° , 90° , and 120°) between the planes of the vaginal tubes and the uterine canal following the anatomical variations from anteversion to retroversion. Holes for dose measurements are situated along the defined lines of reference, with a special hole for rectal measurements which lies



Fig 3 The perspex phantom (For explanation see text)

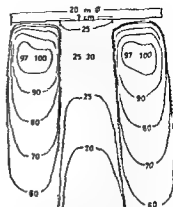


Fig 4 Isodoses of the 31 MeV betatron central shielding Roentgen rays FSD 100 cm

at a minimum of 3 cm from the point of the external os. The doses were measured with a Siemens gammameter. The maximum rectal dose has also been determined with the same Siemens gammameter in a series of 231 consecutive patients with carcinoma of the cervix stage II during the vaginal radium insertion.

The radium doses were also calculated with the help of MEREDITH's (1949) tables. A slight approximation was allowed in the positioning of the intra uterine radium to simplify the calculations but otherwise the conditions matched those of the phantom.

Accuracy of the measurement. Perspex which was used for the phantom is not quite equivalent to tissue as regards dosimetry. However as the present problem concerned doses for clinical purposes perspex seemed satisfactory although polystyrene might have been a better choice of material.

At short distances the relatively small differences in density between perspex and tissue are negligible and even up to 8 cm the heavier absorption in perspex will mostly be counteracted by a higher rate of scattered radiation. With the purposes we had in view we might have measured in free air but a phantom appeared better for achieving the given configurations.

The phantom measurements were checked for reliability in two ways. First by comparing the values obtained from two separate insertions with those from a simultaneous insertion of vaginal and uterine radium. The former happened to exceed the latter by an average of 11 per cent in the area 0 to 2 cm from the level of the external os and by about 4 per cent at the points farther away from the tumour area. As the simultaneous measurements agreed best with the calculated

Table 1

Individual and total doses (in rad) from vaginal radium tubes for the different configurations (see Fig. 1) values calculated at points A B C and D. The numbering of the radium tubes is explained in Fig. 2

Points	Configuration I				Configuration II				Configuration III			
	A	B	C	D	A	B	C	D	A	B	C	D
r ₁	1 670	410	490	260	2 030	640	520	330	1 670	410	490	260
r ₂	1 040	290	440	200	1 040	290	440	200	900	90	340	60
r ₃	670	200	330	160	400	160	260	130	670	200	330	160
Total	3 380	900	1 260	620	3 470	1 090	1 220	660	3 240	700	1 160	480

values, and as the separate measurements must be used for special comparisons, both sets of values were utilized in the results. Secondly, the phantom measurements were tested for reliability by comparing the measured values with the calculated ones. These were in close agreement, with differences from 1 to 5 per cent in both directions.

A comparison of the clinical and phantom rectal doses is given under 'Results'.

Determination of betatron doses. The isodose charts of the two betatrons were used to find the 10 cm depth contribution in the lines of reference. The 31 MeV isodoses with the central shields are given in Fig. 4. The isodoses from the 33 MeV betatron (not shown) were similar. Isodose charts without central shielding were also consulted since part of the treatment was unshielded.

For purposes of comparison, the RBE of the roentgen rays from the betatrons may be set arbitrarily as equal to 0.8. This value lies within the range found by OFTEDAL (1956) and by MOSSIGE (1956), who tested our betatrons, and that reported by KOHN (1958).

Results

Contribution by radium. The doses delivered by the three different vaginal applicators including the contribution by the individual radium tubes, are presented in Table 1. It is evident that with the tubes in the H form (configuration III), the doses at all four points of reference are reduced in comparison to those given by three parallel tubes (configurations I and II). The reduction is considerable at the points corresponding to the pelvic wall (B and D). Configurations I and II produce almost equal doses at all points except point B corresponding to the obturator region, where the latter is obviously most effective.

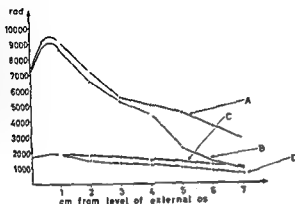


Fig 5 Combined contribution of uterine and vaginal applicators at the respective lines of reference

A — uterine 30 mg vaginal 30 mg 2 cm from uterine cavity

B — uterine 20 mg vaginal 30 mg 2 cm from uterine cavity

C — uterine 30 mg vaginal 30 mg 5 cm from uterine cavity

D — uterine 20 mg vaginal 30 mg 5 cm from uterine cavity

Turning to the relative contribution by the individual tubes the highest difference between tubes r_1 and r_2 lies at point A the difference being less marked at the three points farther away from the tumour area.

The individual contributions of the two uterine applicators are shown in Table 2. The doses from vaginal and uterine applications combined are given graphically in Fig 5. With 20 mg of radium instead of 30 mg in the uterine cavity there is a considerable difference in the dose at the median line of reference more than 4 cm away from the fornix. This corresponds to the upper part of the uterine surface which is relatively unimportant therapeutically. The total contribution does not exceed 2000 rad along the pelvic wall line and the difference between the two combinations is below 500 rad at all the points. The rapid fall in dose between the median and lateral lines at the 0 to 3 cm levels is also worth noting as this corresponds to the common area of tumour spread.

In Table 3 the relative individual contributions of the vaginal and uterine applications are recorded. Both contribute about equally to the total dose at point A. The vaginal contribution along the pelvic wall varies from 64 per cent in the obturator region to 50 per cent in the iliac region when the uterus contains 20 mg radium. With 30 mg radium in the uterus the relative vaginal contribution is slightly lower but it does not fall below 40 per cent of the total dose in the area measured.

The doses measured in the phantom in the ante- and retroverted uterine positions were little different from those in the median position. The rectal doses were however higher with a retroverted uterus. Considering the true anatomy in which the positioning of the uterus does not influence the conditions of the pelvic wall it is likely that intra uterine radium in the anteverted position will produce a higher relative contribution to the common and external iliac areas.

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Table 5

Contribution of vaginal radium (in per cent) to total maximum rectal dose (in rad) at separate insertions with 30 mg vaginal and 30 mg uterine radium

	Rad	Per cent
Anteversion	2 930/4 300	69
Med an position	2 950/4 550	65
Retroversion	2 900/4 800	61

The 31 and 33 MeV betatrons produced almost equal results in the plane of reference the difference being less than 100 rad at 75 per cent of the points and nowhere exceeding 300 rad. The dose distribution is also fairly homogeneous being about 3 500 rad along the pelvic wall, and about 3 000 rad in the median line of reference.

As mentioned previously, the betatron doses to the periphery were raised in 1960. The pelvic wall doses should be reduced by 20 per cent to correct for patients treated between 1958 and 1960 (with the 31 MeV machine only).

Fig 6 giving betatron rodoses in two patients of different body size are presented both to illustrate the dose distribution in anatomical sections and to demonstrate individual differences.

Discussion

Radiation treatment has developed from an empirical art to a science of dosimetry the aim now being to eradicate the primary tumour and destroy possible pelvic metastases while protecting vital structures from radiation injury. The ways to achieve this differ slightly among the various treatment systems.

In the Manchester system the need for individual dosimetry is stressed. According to TOD & MEREDITH (1953) the optimum dose to point A from radium is 8 000 rad delivered in two three day sessions (total 144 hours) but only 6 500 rad if the patient is over 65 years old or if supplementary roentgen rays are given. KOTTMEIER (1954) has stated that in the Stockholm method the radium contribution to point A does not exceed 6 500 rad delivered in 50 to 60 hours. In the Oslo system described in this paper the point A dose varies from 6 500 to 7 200 rad delivered in 120 to 240 hours. The rule in recent years has been 240 hours that is two separate insertions. The dose rates must be taken into account in comparing the effect of the different systems.

Table 2

Individual contribution (in rad) from the two types of uterine applicators at different points

Active length	Points			
	A	B	C	D
44 mm	3 150	630	3 150	630
68 mm	3 790	880	3 790	880

Table 3

Relative individual contributions (in per cent) from vaginal and uterine applicators. The values indicate the vaginal dose as a percentage of the total. Vaginal configuration I is combined with both types of uterine applicators

		Vaginal 30 mg uterine 20 mg		Vaginal 30 mg uterine 30 mg	
Distances from uterine axis		5 cm	2 cm	2 cm	5 cm
Distance from plane of fornix	6 cm	50	47	21	40
	5 cm	53	31	21	42
	4 cm	50	29	26	41
	3 cm	54	34	33	49
	2 cm	57	52	47	51
	1 cm	64	67	66	58

Table 4

Maximal rectal doses (in rad) with simultaneous insertions in different uterine positions

	Vaginal 30 mg uterine 20 mg		Vaginal 30 mg uterine 30 mg	
Anteversion	3 150		Not measured	
Median position	3 450		3 800	
Retroversion	3 700		4 000	

The rectal doses measured in the phantom are the least reliable from the anatomical point of view. The results are recorded in Tables 4 and 5. The maximum rectal doses in 231 patients with cervical carcinoma stage II during vaginal radium insertion were $2\,550 \text{ rad} \pm 700 \text{ rad}$ (mean and standard deviation); this agrees well with the phantom dose of $2\,950 \text{ rad}$.

Contribution by external radiation. The estimated dose at the mid pelvis was $2\,000 \text{ rad}/40 \text{ days}$ with 170 kV roentgen rays as used prior to 1958.

do e It must also be remembered that the point of the maximum dose in the rectum may be different in the uterine and vaginal applications, which again reduces the risk of rectal damage Experience also suggests that the rate of complications in the Oslo system is reasonably low and that it appears to be dose rate dependent (BERGSJØ & EVANS 1964)

Regarding external treatment both KOTTMEIER (1963) and TOD & MEREDITH (1953) agree that the dose to the parametrium should be 3 000 R/four weeks KOTTMEIER increases this dose to 5 000 R in advanced cases The betatron contribution to the parametrium in the Oslo system is about 3 500 rad but a direct comparison is difficult to make because of the uncertainty of the relative biologic effectiveness

Without going into details we should like to point out that the Oslo system is well tolerated although the patients are confined to bed for two periods of five days Complications requiring interruption of the radium insertions are exceptional With regard to radiation hygiene the operators and technical staff handling the radium during the actual insertions receive smaller doses in the Oslo system from each application than from the larger amounts of radium used in the other systems Although members of the nursing staff come into contact with the patients several times a day constant dosimetry has revealed that they and the personnel in charge of the radium applications are kept well below the permissible tolerance limits of radiation (GRANDE & JAHREX 1965) From this point of view the ideal is an automatic loading system

Acknowledgement

This investigation was in part supported by a grant from the Alexander Malthe's legacy sponsored by Oslo Surgical Society The perspex phantom was made at the Norsk Hydro Institute for Cancer Research Dr Bergsjø was a fellow of the Norwegian Cancer Society during this investigation

SUMMARY

The Norwegian system of radiation treatment for carcinoma of the uterine cervix is described in detail The order of magnitude of the pelvic doses has been determined with the help of a perspex phantom standard calculation tables and clinical measurements The system is compared to the Manchester and Stockholm systems with special reference to the different dose rates of the radium applications

ZUSAMMENFASSUNG

Die norwegische Methode der Strahlentherapie des Uteruskarzinomes wird eingehend beschrieben Die Größe der Beckendosen wurde mit Hilfe eines Perspexphantomes mittels Standardrechentabellen und klinischen Messungen ermittelt Das System wird mit den Manchester und Stockholm Systemen verglichen Besondere Beachtung wird den verschiedenen Intensitäten der Radiumstrahlenkörper geschenkt

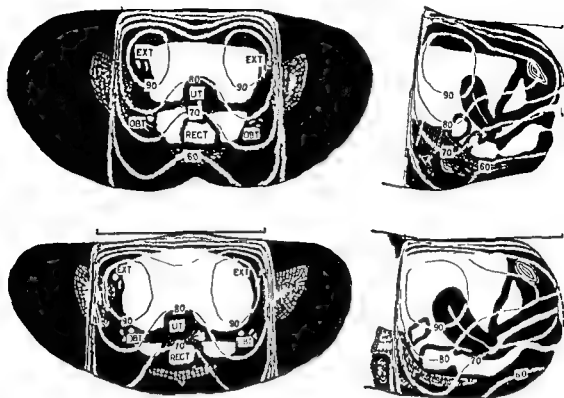


Fig 6 Isodoses from 33 MeV betatron roentgen rays pelvic fields 16 cm x 16 cm resulting from 200 R x 12 unshielded and 200 R x 13 with shielding of the lower central part of the field all treatments given from the front Cross and sagittal sections in two patients of different body size

ELLIS (1963) has shown that the doses producing the same effect with different times are connected by the relationship

$$\frac{D_1}{D_2} = \left(\frac{T_1}{T_2} \right)^{0.6}$$

With this formula, the dose range at point A according to the Oslo system is equivalent to 5 700 to 6 300 rad in the Manchester system and to 4 500 to 5 000 rad in the Stockholm system, indicating that the dose effect of the Oslo system with two separate radium insertions is probably slightly lower at point A as compared to the two former systems

KOTTMEIER (1963) paid much attention to the doses in the bladder and rectum and stated that these should not exceed 5 500 R and 4 000 R respectively (1 R = 0.97 rad). The rectal dose of the Oslo system lies between 4 300 and 4 800 rad/240 hours, which, with Ellis formula produces the same effect as 3 000 to 3 350 rad/60 hours, or considerably below the permissible maximum

ENDOCURIETHERAPY — A DOSIMETRIC STUDY OF TWO PARALLEL RADIOACTIVE SOURCES

by

B PIERQUIN A DUTREIX C PAINE D CHASSAGNE and A WAMBERSIE

The basic principles of our new method for endocurietherapy (this term refers to implants of radioactive isotopes into the tissues) were outlined in a recent article (PIERQUIN & DUTREIX 1967). Although the final analysis of dosimetry is made from the actual distribution of the radioactive material in the patient it is necessary to develop a preliminary distribution plan to help the radiotherapist to plan the optimum arrangement in given circumstances. Some basic information for the preliminary distribution plan is developed in the present paper and represents a systematic study of the dosimetry around two straight parallel radioactive sources of equal length. Our work will subsequently be extended to cover the varying clinical and geometric conditions that can be foreseen and rules for the optimum distribution of the radioactive material will then be set up.

Methods

The calculations were made by computer the dose being calculated at 1 500 points around the sources for each plane of interest and at the desired degree of magnification of the calculated plane with respect to the size of the source (DUTREIX 1967) (Fig 1).

Submitted for publication 11 September 1967

RÉSUMÉ

Les auteurs décrivent en détail la méthode norvégienne de traitement par les radiations du cancer du col de l'utérus. L'ordre de grandeur des doses pelviennes a été déterminé sur un fantôme en perspex avec des tables de calcul standard et par des mesures cliniques. Cette méthode est comparée aux méthodes de Manchester et de Stockholm en particulier en ce qui concerne les doses différentes d'application de radium.

REFERENCES

- BERGSJØ P and EVANS J C: Late radiation reactions in cancer of the cervix. *Acta obstet gynec scand* 43 (1964) Suppl No 7 p 90
- DAILEY T: Combined radiological surgical treatment of carcinoma of the cervix. *Surg Gynec Obstet* 108 (1959) 600
- ELLIS F: Fractionation and dose rate. I. The dose time relationship in radiotherapy. *Brit J Radiol* 36 (1963) 153
- GRANDE P: Calculation and measurement of doses from a radium applicator for treatment of cancer in the uterine cervix. *Brit J Radiol* 31 (1958) 336
- and JAHREN R: Reduction of personnel exposure in the Norwegian Radium Hospital 1954—1963. *Acta radiol Ther Phys Biol* 3 (1965) 12
- KOHN H I: The relative biological effectiveness of external beams of ionizing radiations. In: *Progress in radiation therapy* (1958) pp 62—99. Edited by F. Buschke. Grune & Stratton, New York 1958
- KOLLER O: A comparison between the results of irradiation therapy alone and individualized radiological and surgical treatment of cervical carcinoma stage I. *Acta obstet gynec scand* 43 (1964) Suppl No 7 p 68
- KOTTMEIER H L: Modern trends in the treatment of cancer of the cervix. *Acta radiol* (1954) Suppl No 116 p 405
- : Radiation therapy in cervical carcinoma. *Triangle (Sandoz)* 6 (1963) 11
- MEREDITH W J: Radium dosage. The Manchester system. Livingstone Ltd, Edinburgh 1949
- MOSSIGE J: The relative biological efficiency of 31 MeV betatron γ irradiation and 176 keV γ rays as measured by recessive sex linked lethals in *drosophila melanogaster*. In: *Progress in radiobiology. Proc 4th Internat Confer Radiobiology* Cambridge 1955 pp 137—143. Oliver & Boyd, Edinburgh 1956
- OPTEDAL P: The relative biological efficiencies of 31 MeV betatron γ radiation and 175 keV γ rays as measured by lethal effects on 4 day old chick embryos. In: *Progress in radiobiology. Proc 4th Internat Confer Radiobiology* Cambridge 1955 pp 131—136. Oliver & Boyd, Edinburgh 1956
- SCHJØTT RIVERS E: Can the results of irradiation in cancer of the uterine cervix be improved by prophylactic hysterectomy? *Acta obstet gynec scand* 31 (1951) Suppl No 7
- TOD M C and MEREDITH W J: Treatment of cancer of the cervix uteri — a revised Manchester method. *Brit J Radiol* 26 (1953) 252

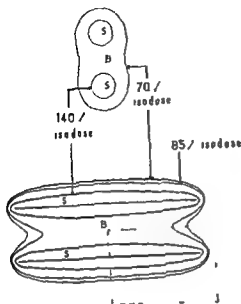


Fig 2 Reconstruction of the complete plane (cf fig 1) The 140% isodose encloses the high dose zone corresponding to a reference isodose of 70%. The example taken is for 6 cm sources separated by 1.68 cm. The basal dose (B) is 671 rad per 24 hours.

separation = the separation of the sources has been taken to vary between 0.8 cm and 2.1 cm

The reasons for these choices of length and separation are discussed below

The terms for the treatment volume are defined as follows

basal dose = the maximum dose in the plane of the two sources midway between them and equidistant from their ends

reference isodose (RI) = the isodose corresponding to the envelope enclosing the treatment volume (we have studied two treatment volumes enclosed by reference isodose whose values are 85% and 70% of the basal dose respectively RI 85% and RI 70%)

high dose zone = that zone of high dosage surrounding each source which is enclosed by the isodose whose value is twice that of the reference isodose (Fig 2)

length = the distance between the limits of the treatment volume in its axis parallel to equidistant from and in the same plane as the source

width = the distance between the limits of the treatment volume in that axis which lies in the same plane as the sources but perpendicular to them

thickness = the distance between the limits of the treatment volume in the plane perpendicular to the sources and equidistant from them which is situated midway between their ends (Fig 3)

Under the conditions actually studied of the active length and separation of

B.

CALCUL NO 1
PLAN DE COUPE PARALLELE AU PLAN OX OY A 0 0 CM DE CE PLAN
FILIN PASSANT PAR LES FILS
COORDONNEES DU PREMIER POINT CALCULE

AGRANDISSEMENT 5 00

	XC	0 0	CM
671	670	667	663
679	678	676	671
705	704	701	697
752	751	748	743
827	826	823	818
944	943	940	936
1133	1132	1129	1125
1444	1443	1441	1438
2156	2155	2152	2148
3599	3599	3597	3593
5599	5599	5597	5593
8116	8115	8113	8109
10812	10811	10809	10805
13613	13612	13610	13606
16518	16517	16515	16511
19423	19422	19420	19416
22328	22327	22325	22321
25233	25232	25230	25226
28138	28137	28135	28131
31043	31042	31040	31036
33948	33947	33945	33941
36853	36852	36850	36846
39758	39757	39755	39751
42663	42662	42660	42656
45568	45567	45565	45561
48473	48472	48470	48466
51378	51377	51375	51371
54283	54282	54280	54276
57188	57187	57185	57181
60093	60092	60090	60086
62998	62997	62995	62991
65903	65902	65900	65896
68808	68807	68805	68801
71713	71712	71710	71706
74618	74617	74615	74611
77523	77522	77520	77516
80428	80427	80425	80421
83333	83332	83330	83326
86238	86237	86235	86231
89143	89142	89140	89136
92048	92047	92045	92041
94953	94952	94950	94946
97858	97857	97855	97851
100763	100762	100760	100756
103668	103667	103665	103661
106573	106572	106570	106566
109478	109477	109475	109471
112383	112382	112380	112376
115288	115287	115285	115281
118193	118192	118190	118186
121098	121097	121095	121091
124003	124002	124000	123996
126908	126907	126905	126901
129813	129812	129810	129806
132718	132717	132715	132711
135623	135622	135620	135616
138528	138527	138525	138521
141433	141432	141430	141426
144338	144337	144335	144331
147243	147242	147240	147236
150148	150147	150145	150141
153053	153052	153050	153046
155958	155957	155955	155951
158863	158862	158860	158856
161768	161767	161765	161761
164673	164672	164670	164666
167578	167577	167575	167571
170483	170482	170480	170476
173388	173387	173385	173381
176293	176292	176290	176286
179198	179197	179195	179191
182103	182102	182100	182096
185008	185007	185005	185001
187913	187912	187910	187906
190818	190817	190815	190811
193723	193722	193720	193716
196628	196627	196625	196621
199533	199532	199530	199526
202438	202437	202435	202431
205343	205342	205340	205336
208248	208247	208245	208241
211153	211152	211150	211146
214058	214057	214055	214051
216963	216962	216960	216956
219868	219867	219865	219861
222773	222772	222770	222766
225678	225677	225675	225671
228583	228582	228580	228576
231488	231487	231485	231481
234393	234392	234390	234386
237298	237297	237295	237291
240203	240202	240200	240196
243108	243107	243105	243101
246013	246012	246010	246006
248918	248917	248915	248911
251823	251822	251820	251816
254728	254727	254725	254721
257633	257632	257630	257626
260538	260537	260535	260531
263443	263442	263440	263436
266348	266347	266345	266341
269253	269252	269250	269246
272158	272157	272155	272151
275063	275062	275060	275056
277968	277967	277965	277961
280873	280872	280870	280866
283778	283777	283775	283771
286683	286682	286680	286676
289588	289587	289585	289581
292493	292492	292490	292486
295398	295397	295395	295391
298303	298302	298300	298296
301208	301207	301205	301201
304113	304112	304110	304106
307018	307017	307015	307011
309923	309922	309920	309916
312828	312827	312825	312821
315733	315732	315730	315726
318638	318637	318635	318631
321543	321542	321540	321536
324448	324447	324445	324441
327353	327352	327350	327346
330258	330257	330255	330251
333163	333162	333160	333156
336068	336067	336065	336061
338973	338972	338970	338966
341878	341877	341875	341871
344783	344782	344780	344776
347688	347687	347685	347681
350593	350592	350590	350586
353498	353497	353495	353491
356403	356402	356400	356396
359308	359307	359305	359301
362213	362212	362210	362206
365118	365117	365115	365111
368023	368022	368020	368016
370928	370927	370925	370921
373833	373832	373830	373826
376738	376737	376735	376731
379643	379642	379640	379636
382548	382547	382545	382541
385453	385452	385450	385446
388358	388357	388355	388351
391263	391262	391260	391256
394168	394167	394165	394161
397073	397072	397070	397066
399978	399977	399975	399971
402883	402882	402880	402876
405788	405787	405785	405781
408693	408692	408690	408686
411598	411597	411595	411591
414503	414502	414500	414496
417408	417407	417405	417401
420313	420312	420310	420306
423218	423217	423215	423211
426123	426122	426120	426116
429028	429027	429025	429021
431933	431932	431930	431926
434838	434837	434835	434831
437743	437742	437740	437736
440648	440647	440645	440641
443553	443552	443550	443546
446458	446457	446455	446451
449363	449362	449360	449356
452268	452267	452265	452261
455173	455172	455170	455166
458078	458077	458075	458071
460983	460982	460980	460976
463888	463887	463885	463881
466793	466792	466790	466786
469698	469697	469695	469691
472603	472602	472600	472596
475508	475507	475505	475501
478413	478412	478410	478406
481318	481317	481315	481311
484223	484222	484220	484216
487128	487127	487125	487121
490033	490032	490030	490026
492938	492937	492935	492931
495843	495842	495840	495836
498748	498747	498745	498741
501653	501652	501650	501646
504558	504557	504555	504551
507463	507462	507460	507456
510368	510367	510365	510361
513273	513272	513270	513266
516178	516177	516175	516171
519083	519082	519080	519076
521988	521987	521985	521981
524893	524892	524890	524886
527798	527797	527795	527791
530703	530702	530700	530696
533608	533607	533605	533601
536513	536512	536510	536506
539418	539417	539415	539411
542323	542322	542320	542316
545228	545227	545225	545221
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559753	559752	559750	559746
562658	562657	562655	562651
565563	565562	565560	565556
568468	568467	568465	568461
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574278	574277	574275	574271
577183	577182	577180	577176
580088	580087	580085	580081
582993	582992	582990	582986
585898	585897	585895	585891
588803	588802	588800	588796
591708	591707	591705	591701
594613	594612	594610	594606
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600423	600422	600420	600416
603328	603327	603325	603321
606233	606232	606230	606226
609138	609137	609135	609131
612043	612042	612040	612036
614948	614947	614945	614941
617853	617852	617850	617846
620758	620757	620755	620751
623663	623662	623660	623656
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629473	629472	629470	629466
632378	632377	632375	632371
635283	635282	635280	635276
638188	638187	638185	638181
641093	641092	641090	641086
643998	643997	643995	643991
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649808	649807	649805	649801
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670143	670142	670140	670136
673048	673047	673045	673041
675953	675952	675950	675946
678858	678857	678855	678851
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684668	684667	684665	684661
687573	687572	687570	687566
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693383	693382	693380	693376
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699193	699192	699190	699186
702098	702097	702095	702091
705003	705002	705000	704996
707908	707907	707905	707901
710813	710		

Table 1

Treatment volumes having same length and width

Length or width (cm)	Separation of sources (cm)	
	RI 70 %	RI 85 %
2.0	1.1	1.2
2.5	1.3	1.5
3.0	1.6	1.8
3.5	1.9	

B Relations between the width of the treatment volume and the radioactive material

1 *Separation* Width of treatment volume/separation of sources = 1.75 at RI 85 % and 1.90 at RI 70 %

2 *Active length* The width of the treatment volume remains almost independent of the active length for the same separation of the sources

C Relations between thickness of treatment volume and radioactive material

1 *Separation* Thickness of treatment volume/separation of sources = 0.5 at RI 85 % and 0.85 at RI 70 %

2 *Active length* The thickness of the treatment volume increases slightly as the active length of the sources increases from 1 to 10 centimetres from 0.46 to 0.59 at the 85 % isodose and from 0.77 to 0.92 at the 70 % isodose)

Inter relations between the dimensions of the treatment volume

1 Width and thickness

From relations B 1 and C 1 above it is evident that width and thickness are linked within the limits studied thus width/thickness at RI 85 % = 3.5 and at RI 70 % = 2.3

There is some variation in these values as the active lengths vary from 1 to 10 centimetres from 3.9 to 3.0 at the 85 % isodose and from 2.5 to 2.1 at the 70 % isodose

2 Length and width

There is a useful relation between the length and the width of the treatment volume. If the width of the treatment volume is small the isodoses are such that the width is numerically greater than the length implying that the sources may be more effectively placed perpendicular to the long axis of the treatment

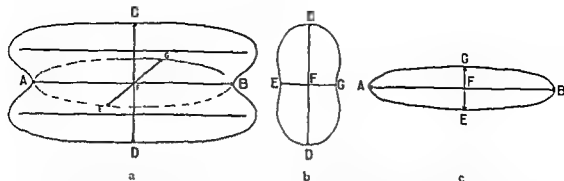


FIG. 3 Dimensions of the treatment volume the figure being to scale for the 70 % isodose around 6 cm long sources separated by 1.68 cm. a) Composite view showing the three dimensions length (AB), width (CD), thickness (FG), all taken through the central point (F), the position of the basal dose. b) and c) show the two planes perpendicular to ABCD.

sources, the dose rate calculated at the reference isodose varied between 750 and 1 500 rad per day when using iridium 192 wire of a linear activity between one and two millicuries per centimetre. The total tumour dose at the reference isodose is generally taken as 7 500 rad for lesions treated solely by implants (PIFRQUIN & DUTREIX 1967). This dose is delivered more rapidly for small volumes. No correction is at present applied to attempt theoretical equivalence of biological effect to 7 day treatments. The calculations have been made on the basis of placing the radioactive material in tissue (density = 1), a correction for attenuation in the tissues, according to measurements recently published (MEISBERGER & SHATEK 1965, MEREDITH, GIFFEN & KAWASHIMA 1966), has been applied.

Relations between treatment volume and radioactive material

The dimensions of the treatment volume are simply related to the active length and separation of the sources. Within the limits set, the length is determined only by the active length, and the width and thickness by the separation of the sources.

A. Relations between length of treatment volume and sources

1 *Active length* Length of treatment volume: active length of sources = 0.7 at RI 85 % and 0.9 at RI 70 %.

These values increase slightly as the active lengths increase from 1 to 10 centimetres, from 0.65 to 0.75 at the 85 % isodose and from 0.88 to 0.94 at the 70 % isodose.

2 *Separation* The length of the treatment volume is virtually independent of the separation of the sources.

Table 1

Treatment volumes having same length and width

Length or width (cm)	Separation of sources (cm)	
	RI 10	RI 85
2.0	1.1	1.2
2.5	1.3	1.5
3.0	1.6	1.8
3.5	1.9	

B Relations between the width of the treatment volume and the radioactive material

1 *Separation* Width of treatment volume/separation of sources = 1.75 at RI 85 % and 1.90 at RI 70 %

2 *Active length* The width of the treatment volume remains almost independent of the active length for the same separation of the sources

C Relations between thickness of treatment volume and radioactive material

1 *Separation* Thickness of treatment volume/separation of sources = 0.5 at RI 85 % and 0.85 at RI 70 %

2 *Active length* The thickness of the treatment volume increases slightly as the active length of the sources increases from 1 to 10 centimetres from 0.46 to 0.59 at the 85 % isodose and from 0.77 to 0.92 at the 70 % isodose)

Inter relations between the dimensions of the treatment volume

1 Width and thickness

From relations B-1 and C-1 above it is evident that width and thickness are linked within the limits studied thus width/thickness at RI 85 % = 3.5 and at RI 10 % = 2.3

There is some variation in these values as the active lengths vary from 1 to 10 centimetres from 3.9 to 3.0 at the 85 % isodose and from 2.5 to 2.1 at the 70 % isodose

2 Length and width

There is a useful relation between the length and the width of the treatment volume. If the width of the treatment volume is small the isodoses are such that the width is numerically greater than the length implying that the sources may be more effectively placed perpendicular to the long axis of the treatment

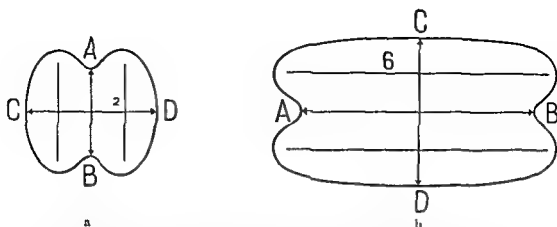


Fig. 4. Relation between length and width of a treatment volume enclosed by the 10% reference isodose: a) With 2 cm long sources separated by 1.46 cm. The treatment volume is only 1.8 cm long (AB) and 2.7 cm wide (CD). b) With 6 cm long sources separated by 1.68 cm. This situation is reversed: length of treatment volume is 3.9 cm (AB) and width 3.0 cm (CD).

volume. After a certain critical combination of the length of the treatment volume and the separation of the sources this situation is reversed. In practice, this concept is of value only for sources up to 4 cm long, with greater active lengths, the separation which would be necessary to make the width of the treatment volume its largest dimension would be unacceptably great (Table 1).

Fig. 4 shows the situation as it applies to 2 cm and 6 cm long sources. Table 1 provides more specific data in the clinically important region. The separation values set out in the table are those which correspond to treatment volumes whose length and width are equal at the values shown. Thus if the desired actual separation is less than the value shown, the sources should be placed as in Fig. 4b but if it exceeds this value as in Fig. 4a. Treatment volumes less than 2 cm long are always treated with transverse sources (Fig. 4a) and those more than 3.5 cm long always with longitudinal sources.

3. Thickness of treatment volume and diameter of the high dose zone

If one takes the smallest treatment volume (active length of sources 1 cm, separation 0.33 cm, reference isodose 85%) and the largest volume (active length 10 cm, separation 2.1, reference isodose 70%), then for the same linear activity (but a different brachy dose) the respective diameters of the high dose zones are as follows:

	Thickness	Diameter of high dose zone
Smallest volume	0.36 cm	0.35 cm
Largest volume	1.80 cm	0.97 cm

Table 2

Active length of sources (cm)	Separation of sources (cm)			
	0.8	0.9	1.0	1.1
1	1.1	1.2	1.3	1.3
2	1.2	1.3	1.4	1.6
3	1.2	1.3	1.5	1.7
4	1.3	1.4	1.6	1.8
5	1.3	1.4	1.6	1.9
6	1.3	1.5	1.7	1.9
7	1.3	1.5	1.7	2.0
8	1.3	1.5	1.7	2.0
9	1.3	1.5	1.8	2.1
10	1.3	1.5	1.8	2.1
Total dose (rad/h) for a 1 cur activity of 10 mCi/cm using iridium 192				
	40	35	30	25

Discussion

We have taken the active lengths of the sources to vary from 1 to 10 centimetres because these are the usual lengths required in practice. It might well be necessary to increase the length beyond 10 cm for special reasons: if so the separation of two sources should still not exceed 2.1 cm.

The upper and lower limits which we have chosen for the separation of sources are justified as follows. The upper limit 2.1 cm corresponds to a high dose zone almost 1 cm in diameter with 10 cm long sources and using the 70% isodose. In the present state of our experience we do not like to exceed this diameter and we have the impression that tissue repair becomes much more difficult (with excessive risk of necrosis) when a cylinder of tissues receiving more than 15 000 rad does exceed it. The lower limit of separation is justified by the fact that very narrow thin lesions are best treated by a single line source.

The separations between the sources which we have selected for study have been greater as the active lengths have increased for these three reasons:

Physical fact: the diameter of an isodose round a radioactive line source increases more rapidly with increase in active length the further the isodose considered is situated from the source (PIERQUIN & DUTREIX 1967).

Technical reason: it is difficult to ensure that long wire sources are parallel and there is a greater risk of the hot and cold areas of the separations becoming too small.

Clinical practice the thickness of the treatment volume tends to increase with its length, and this implies a greater separation.

The separation has been further limited in order to ensure that the dose rate falls within reasonable limits for the linear activity of source commonly used. In practice, we try to limit the separation to the values shown for each active length in Table 2. The resulting brachy dose rates for iridium 192 wire of linear activity 1.0 mCi/cm are shown at the top of each column. It is emphasized that these limits, with the exception of the minimum (0.8 cm) and the maximum (2.1 cm) values justified above are, at present, purely empirical.

The dimensions which we have chosen to define the treatment volume are useful in practice, though it must be remembered that in reality this volume has a complex outline somewhat resembling an ellipsoid. The three dimensions chosen have this in common: they all pass through the centre of the treatment volume where the brachy dose is calculated (Fig. 3). The radiotherapist must however remember that the given dimensions do not describe a cuboid form, and must plan his treatment volume to the existing target volume accordingly.

From our data, the smallest volume suitable for treatment by two straight parallel sources measures 0.4 cm \times 0.7 cm \times 1.4 cm and the largest volume 1.8 cm \times 4.1 cm \times 9.0 cm. Because of the limits, which are imposed for the reasons mentioned above, on the separation of sources, however, not all volumes lying between these outside values may be so treated. Whether or not any given volume is acceptable can be determined from the relationships set out above and in Table 2. If the width limit is exceeded additional lines are required in the same plane, and if the thickness limit is exceeded more planes are required.

Although it would be possible to propose rules for the optimum distribution of two straight parallel sources in treatment volumes suitable for treatment by them, this is better left until a study of the more complex arrangements which are useful in practice has been completed.

Conclusions

The systematic study now reported upon, concerned with the dosimetry around two straight, parallel radioactive sources of equal length, formed the first stage in a theoretical analysis of the methods used in our system of curietherapy. The aim of the analysis has been to provide information necessary for the formulation of rules for a preliminary distribution plan which will enable the techniques used to be applied to the best physical advantage. Extensive calculations have been made by the aid of a computer. Simple relationships between the dimensions of the treatment volume and the disposition of the radioactive material were revealed. These relationships will form a fundamental starting point for the study of more complex arrangements.

SUMMARY

A systematic study of the dosimetry around two straight parallel radioactive sources of equal length has been made by the aid of a computer with the aim to provide basic information for setting up preliminary distribution plans enabling the techniques used in curietherapy to be applied to the best advantage. Simple relationships between the three dimensions of the treatment volume and the disposition of the radioactive material could be established and these will form the fundamental starting point for a study of more complex arrangements.

ZUSAMMENFASSUNG

Eine systematische Studie der Dosimetrie um zwei gerade und parallele radioaktive Quellen von gleicher Länge wurde mit Hilfe von Rechenautomatik durchgeführt. Die Untersuchung hatte zum Zweck fundam. n. t.ale Auskunft zu ermitteln, die zur vorläufigen Dosisplanung geeignet ist, um die Technik der Curitherapie am besten auszunutzen. Es wurden einfache Beziehungen zwischen den drei Dimensionen des Behandlungsvolumen und der Applikation des radioaktiven Materials erreicht, die als fundamentaler Operationsbasis beim Studium von komplizierteren Anordnungen verwendet werden sollen.

RÉSUMÉ

Une étude systématique de la dosimétrie autour de deux sources radioactives droites et parallèles de même longueur a été effectuée et constitue le premier chapitre des applications pratiques d'un nouveau système de curietherapie. Des relations simples ont été mises en évidence entre les trois dimensions du volume traité et le matériel radioactif. Ces relations constituent une base de départ fondamentale pour les études dosimétriques de dispositifs radioactifs plus complexes.

REFERENCES

- DUTREIX A. Utilisation d'un ordinateur pour la dosimétrie en curietherapie. *Ann. Physiol. Biol. Méd.* 2 (1967) 139.
- MEISSNER L. L. and SHALEK R. J. The effective absorption of the gamma rays from radium 226, gold 198, cesium 137 and iridium 192 in water. Presented at the Fifty first Annual Meeting of the Radiological Society of North America, Chicago 1965.
- MEREDITH W. J., GREEN D. and KAWASUMI A. The attenuation and scattering in a phantom of gamma rays from some radionuclides in mould and interstitial gamma ray therapy. *Brit. J. Radiol.* 39 (1966) 280.
- FERGUSON B. Précis de curietherapie 1ère édition. Masson & Cie Paris 1964.
- and DUTREIX A. Towards a new system in curietherapie. *Brit. J. Radiol.* 40 (1967) 184.

UPTAKE OF COLLOIDAL CHROMIC PHOSPHATE IN THE MEDIASTINAL LYMPH NODES

Therapeutic possibilities

by

L. J. ANCHUTSI

Reports on the uptake of radioisotopes in the lymph nodes, and in the mediastinal lymph nodes in particular, are scarce, as compared to the extensive literature in the whole field of nuclear medicine. WALKER (1950) demonstrated that the phagocytes of the lymph nodes are very efficient in removing large particle colloids injected into the afferent lymphatic vessels. A few years later, HAIN et coll (1953) described the therapeutic use of intrabronchially instilled silver coated radiogold, but the extremely variable distribution of radioactive material in tissues, and the widely differing activities exhibited by the different lymph nodes, would seem to leave the efficacy of this technique in doubt. HO CHOI et coll (1965) tested intrapleural injection of radiogold as a scanning technique for use in the study of the mediastinal lymphatics in animals. Their results indicated that sufficient time must be allowed for the radiocolloid to enter the lymphatics, the activity did not exceed 5 per cent of the dose injected. MUIER (1956), after intraperitoneal injection in a patient reported that a considerable amount of radiogold was detected in the mediastinal lymph nodes.

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Table 1

Radioactivity distribution of ^{51}Cr labelled chromic phosphates in per cent of the injected dose (particulate chromic phosphate particle size 0.6 to 2 μ colloidal chromic phosphate particle size 0.1 to 0.2 μ)

	At 1 day after injection				At 7 days after injection			
	Particulate chromic phosphate		Colloidal chromic phosphate		Particulate chromic phosphate		Colloidal chromic phosphate	
	Intra venous	Intraperitoneal	Intra venous	Intraperitoneal	Intra venous	Intraperitoneal	Intra venous	Intraperitoneal
Liver	46.6	6.6	80.9	50.5	47.2	4.6	86.1	64.4
Spleen	4.5	1.7	2.6	1.3	5.4	1.1	2.4	1.4
Lung	8.0	0.1	0.2	0.1	1.9	0.8	0.1	0.1
Skeleton	4.0	0.4	2.9	0.3	7.8	0.3	0.9	1.9

no quantitative estimate of the distribution in other regions of the body was published.

A new radiocolloid for intracavitary radiotherapy has previously been described (ANGHILERI *et al.* 1967). This compound of gelatin chromic phosphate has all the characteristics of a true colloidal solution (particle size 0.1 to 0.2 μ).



Figure 1 shows the radioactive distribution at 24 hours after intraperitoneal injection of 50 μCi of ^{51}Cr labelled colloidal chromic phosphate. Two regions of uptake may be noted: liver-spleen-pancreas area and the thymus-mesenteric lymph nodes.

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Reports on the uptake of radioisotopes in the lymph nodes, and in the mediastinal lymph nodes in particular, are scarce as compared to the extensive literature in the whole field of nuclear medicine. WALKER (1950) demonstrated that the phagocytes of the lymph nodes are very efficient in removing large particle colloids injected into the afferent lymphatic vessels. A few years later, HAHN et coll (1953) described the therapeutic use of intrabronchially instilled silver coated radiogold, but the extremely variable distribution of radioactive material in tissues, and the widely differing activities exhibited by the different lymph nodes, would seem to leave the efficacy of this technique in doubt. HO CUIOT et coll (1965) tested intrapleural injection of radiogold as a scanning technique for use in the study of the mediastinal lymphatics in animals. Their results indicated that sufficient time must be allowed for the radiocolloid to enter the lymphatics, the activity did not exceed 5 per cent of the dose injected. MULLER (1956), after intraperitoneal injection in a patient reported that a considerable amount of radiogold was detected in the mediastinal lymph nodes,

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Table 2 (cont.)

After 7 days		
Papain and colloidal chromic phosphate injection after 10 minutes	Colloidal chromic phosphate	Colloidal chromic phosphate and papain injection after 20 minutes
1.96	0.81	1.47
22.88	27.87	14.43
3.36	0.98	2.47
2.59	1.08	1.34
19.79	6.97	5.08

proposed as a therapeutic agent (MESNARD & MADELOX 1960, EMELE *et coll* 1966). On this basis an attempt has been made to test the possibility of increasing the particle size *in situ* in order to obtain a higher uptake in the lymph nodes. With this purpose in mind other groups of animals were injected with 2.5 mg of papain in 2.5 ml of saline before or after the radiocolloid injection and radioactivity counting was performed in the same fashion.

The typical distribution of both types of chromic radiophosphate after intravenous and intraperitoneal injections are recorded in Table 1. The radioactivity distribution 24 hours after injection of the radiocolloid is demonstrated by the scintigram p. 203. It may be noted that there are two regions of radioactivity uptake: the liver-spleen-pancreas area and the area of the thymus-mediastinal lymph nodes (indicated by the arrow). After dissection the separated counting in the mediastinal lymph nodes and the thymus showed a ratio of approximately 70:1 which is an indication that most of the radioactivity is taken up by the lymph nodes. The radioactivity values in different organs and tissues at respectively 1 day and 7 days after intraperitoneal injection of colloidal chromic phosphate are given in Table 2. The effects of pre and post colloidal injections of papain are also recorded in this table.

The radioactivity uptake of the mediastinal lymph nodes (Table 2) is 4 times higher after colloidal chromic phosphate injection than after the particulate type of administration. It should be remembered that the particulate chromic phosphate has a wide range of particle size 0.6 to 2 μ with a predominating size of over 1 μ (ANCHILERE 1965). Some of these particles succeed in reaching the thoracic

Table 2

Radioactivity distribution (in per cent) after injection of ^{51}Cr labelled chromic phosphates and the effects of intraperitoneal injection of papain (all percentages are means of values from three animals)

	After 24 hours		
	Particulate chromic phosphate	Colloidal chromic phosphate	Colloidal chromic phosphate and papain injection after 20 minutes
Spleen	4.13	2.83	2.12
Liver	6.83	44.73	29.74
Intestine	0.21	1.68	4.14
Mesentery	0.32	1.43	2.21
Mediastinal lymph nodes	2.30	9.32	6.80

The uptake of radiocolloids is also largely affected by the route of administration. Colloids of relatively great particle size are mainly deposited in the liver and spleen after intravenous injection, while colloids of smaller particle size are deposited primarily in the bone marrow and spleen and secondarily in the liver (SCHUBERT 1951). When administered intraperitoneally the particulate form of chromic phosphate is pocketed in various areas of the peritoneum, or filtered out by the first lymph nodes encountered because of the too large particle size, whereas the colloidal form is carried over to the lymphatic system. The larger particles originally present in its size spectrum or formed *in vivo* by aggregation of smaller particles are trapped by the first line of lymph nodes, and the remainder go into the thoracic duct, with posterior incorporation into the blood circulation and final removal by the reticulo-endothelial system: liver, spleen and bone marrow.

This paper is a report on experimental work carried out for investigating the fate of ^{51}Cr labelled colloidal chromic phosphate after intraperitoneal injection in rats. Adult albino rats weighing 250 grams were injected with 50 μCi of the agent and sacrificed after 1 day and 7 day intervals. The radioactivity was counted with a well type scintillation counter (Gamma Guard Tracerlab) in various organs and tissues.

In the preliminary experiments *in vitro* tests had shown the colloidal chromic phosphate to precipitate rapidly and completely through the hydrolytic action of papain. The physiologic effects of this enzyme have been intensively studied (HAKIN & PETERS 1962, MORARD *et coll.* 1963, SPICER & BRYAN 1958) and

SUMMARY

The uptake of radioactive colloidal chromic phosphate in the mediastinal lymph nodes was studied after intraperitoneal injection in rats. A significant uptake approx 9% was noted and this can be increased to approx 19% by pre injection of papain. The wider range of action of the new compound of this colloid offers advantages over the particulate form of chromic phosphate for the prophylactic and therapeutic irradiation of tumor cells.

ZUSAMMENFASSUNG

Die Aufnahme von radioaktivem kolloidalem Chrom Phosphat in den mediastinalen Lymphknoten nach intraperitonealer Injektion in Ratten wurde studiert. Signifikant war die beobachtete Aufnahme von 9% und dieser Wert konnte mittels Pre Injektion von Papain bis auf 19% erhöht werden. Der grossere Wirkungsbereich dieser neuen Kolloidenverbindung er bietet Vorteile gegenüber der partikulären Form des Chrom Phosphats besonders bei der prophylaktischen und therapeutischen Bestrahlung von Tumorzellen.

RÉSUMÉ

L'auteur a étudié la fixation du phosphate de chrome colloïdal radioactif dans les ganglions lymphatiques médiastinaux après injection intrapéritonéale sur des rats. Il a constaté une fixation importante d'environ 9% qui peut augmenter jusqu'à 19% environ par injection préalable de papaine. Le plus large domaine d'action de cette nouvelle préparation colloïdale présente des avantages sur la forme en particules du phosphate de chrome pour l'irradiation prophylactique et thérapeutique des cellules tumorales.

REFERENCES

- ANGHILERI L. J. In vivo distribution of radioactive chromic phosphate. Influence of the particle size and route of injection. 15 (1965) 623
- and MARQUEZ R. New colloidal chromic radiophosphate (P 32) for local irradiation of the central nervous system. Int J appl Radiat 18 (1967) 97
- BURGER R. H. Lymph node response to high-dose intralymphatic injection of radiochromic phosphate. Bull N Y Acad Med 40 (1964) 142
- EVELE J. F. SHANAHAN J. and WINBURG M. M. The analgesic antiinflammatory activity of papain. Arch int Pharmacodyn 159 (1966) 216
- HAHN P. F. and CAROTHERS E. L. Lymphatic drainage following intrabronchial instillation of silver coated radioactive gold colloid in therapeutic quantities. J thorac Surg 25 (1953) 265
- HARIN A. A. and PETERS R. L. Enzyme specific action in vivo. I. The action of certain enzymes by the intravenous route. Exp Med Surg 20 (1962) 194
- HO CHOI S. GORDON W. SHIBHAV F. R. and BENDER M. A. Radiosotope scanning of the mediastinal lymphatics in animals. Acta radol Ther Phys Biol 3 (1965) 229
- MESNARD P. M. and MADELOX G. A new form of utilization of papain. Therapeutics prospects. Bull Acad Med (Paris) 144 (1960) 411

duct and are later phagocytized by the mediastinal lymph nodes. In the case of the colloidal type, the range of particle size is much lower (0.1 to 0.2 μ), permitting a larger amount to enter the thoracic duct and later the blood circulation. The radioactivity uptake in the liver corroborated this assumption. The high increase of radioactivity in the mediastinal lymph nodes when papain was injected prior to the colloid (from 9.3 % to 19.3 %) may be explained by an increase in particle size due to enzymatic action. It converts the too small particles of the radiocolloid into particles more easily trapped and phagocytized by the lymph nodes. As may be seen from Table 2, this morphologic change provokes an increase in the lymph node uptake, with a corresponding decrease in the liver. A smaller effect was noted when papain was injected after the administration of the colloid. Presumably, the time elapsed between colloid injection and papain administration was long enough to cause migration of the small particle sized colloid without being affected by the enzyme.

Despite the large amount of radioactivity deposited in the liver, the dose of radiation is considerably less than for the lymph node. We use the formula

$$D = 73.8 C \times \bar{L} \times T$$

in which C = concentration ($\mu\text{Ci}/\text{gram}$), $\bar{L} = 0.70 \text{ MeV}$ (for ^3P), and $T = 10$ days (effective half life), and consider the radioactivity distribution in the fourth column of Table 2 to be the same as for ^3P labelled colloidal chromic phosphate. The dose delivered to the liver and the mediastinal lymph nodes after intraperitoneal injection of 100 μCi will then be

$$\begin{aligned} d_{\text{lymph node}} &= 199,408 \text{ rad} \\ d_{\text{liver}} &= 929 \text{ rad} \end{aligned}$$

This calculation provides an estimate of the high dose of strong beta radiation delivered to the lymph node.

ZIFDMAN (1955), after injection of tumor cells in the mediastinal lymph glands, demonstrated a pathway for mediastinal node involvement. The similarity between the radiocolloid transport by the lymph stream and the lymphatic spread of tumor cells, emphasizes the possibilities of this radiocompound for prophylactic irradiation.

After intralymphatic injections of particulate chromic phosphate (particle size 0.5 to 1.5 μ) BURGER (1964) found that most of the radioactivity was deposited in the lymph node closest to the site of injection. Contrary to this limited range of action, the colloidal chromic phosphate after intracavitary injection permits prophylactic or therapeutic irradiation (when labelled with ^3P) in a wider area of the lymphatic system.

COMBINED EFFECT IN THE RADIOLOGIC AND IMMUNOLOGIC TREATMENT OF A MALIGNANT HOMOGRAFT

by

ENCHI KANO

Many investigations on the radiation dose response relationships in various lines of mammalian cells both benign and malignant have been reported. Since PUCK & MARCUS (1956) reported on the effect of roentgen irradiation of single mammalian cells tested by a colony formation technique *in vitro*, *in vitro* studies have been carried out in order to elucidate mainly the cell intrinsic character of the radiosensitivity. The influence of peripheral factors on cell radiosensitivity have been analysed mainly by *in vivo* studies since HEWITT & WILSON (1959) published their *in vivo* culture method. WHITMORE & TILL (1964) stated that normal and malignant mammalian cells derived from different sources provoked about the same response to ionizing radiation. WILLIAMS & TILL (1966) reported that newly transformed cells derived from polyoma infected cultures of rat embryo cells *in vitro* and the transformed cell lines were characterized by D_0 values that did not differ significantly from those obtained for the original cells although the radiosensitivities of some of these cell lines after more than 35 weeks of culture *in vitro* yielded signifi-

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- MORARD J C, HALPERN H N and ROBERT L Pathological and biochemical changes and immunological modifications determined in the rabbit by repeated injection of papain C R Acad Sci (Paris) 256 (1963) 1169
- MULLER J H Intraperitoneal application of radioactive colloids *In* Therapeutic use of artificial radioisotopes 269 Edited by P F Hahn John Wiley and Sons New York 1956
- SCHUBERT J Estimating radioelements in exposed individuals Part I Radioelement metabolism Nucleonics 8 (1951), 13
- SPICER S S and BRYANT J H Effect of intravenous injection of papain Amer J Path 34 (1958) 61
- WALKER L A Localization of radioactive colloids in lymph nodes J Lab clin Med 36 (1950), 440
- ZEIDMAN I Experimental studies on the spread of cancer in the lymphatic system III Tumor emboli in thoracic duct The pathogenesis of Virchow's node Cancer Res 15 (1955) 719

investigation was 2×10^4 per ml. The prepared cell suspension was divided into 1.5 ml portions for each culture test tube and kept unmoved at 37°C for seven days (monolayer stationary culture).

In vivo culture method and host animals. Our diffusion chamber technique has been described in detail elsewhere (KANO 1965) and summarized diagrammatically (KANO 1967). The porosity selected for the millipore filters was 0.22μ ; these were sealed to the upper and lower surfaces of each acrylic plastic diffusion chamber with 1 plastic acetone glue. The initial cell concentration of the suspension prepared for the *in vivo* dose response investigation was 75×10^4 per ml of which 0.2 ml were injected into each autoclaved diffusion chamber through the small hole radially oriented through the chamber wall and then closed with paraffin. The hosts were male mice of the dd/YF strain 80 to 120 days old in each of which a diffusion chamber was surgically implanted intraperitoneally for 9 days. The dd/YF mice from the Funabashi farms were housed individually. Conventional pellets of mouse feed and water were supplied *ad libitum*.

Immunization procedure. Some of the dd/YF mice were immunized with 3×10^4 Ehrlich cells and others with dd/YF mouse liver tissue 0.4 g by wet weight per mouse.

Male white rabbits were also immunized with either 10^8 Ehrlich cells or dd/YF mouse liver tissue 1.7 g by wet weight per rabbit once a week for five consecutive weeks. The Ehrlich cells used as antigen were homogenized or irradiated with 3000 R (see under heading irradiation procedure) and the dd/YF mouse liver tissue employed as the other antigen was homogenized. One millilitre of Freund's complete adjuvant for each mouse and 2 ml for each rabbit were added to the antigens before subcutaneous injection. Some of the immunized mice were used as hosts for the diffusion chamber implantation and others were cardiopunctured for antiserum collection 10 days after immunization. The immunized rabbits were also cardiopunctured for antiserum collection a week after the last immunization.

Cytotoxic procedures. Two procedures were undertaken as follows:

1. The Ehrlich cells 10^8 in number were suspended in 1 ml of the culture medium added to 0.1 ml of complement (guinea pig serum) which was obtained in lyophilized form for each culture test tube. The inactivated (56 $^\circ\text{C}$ 30 min) antiserum of either the mice or the rabbits was added to each test tube in 10:1:1 and 0.01 volume per cent of the cell suspension. The test tubes were incubated for one day at 37°C whereafter the number of intact cell nuclei were counted. The control experiments were undertaken in the same manner with fresh antiserum without the complement or with inactivated antiserum with fresh serum of non-immunized dd/YF mice.

2. The Ehrlich cells were cultured in sterilized small square bottles 15 mm \times 15 mm \times 3.2 mm; one of the inside walls of which was partly covered with a small piece of coverslip glass 8 mm \times 20 mm in size. Microscopic observation of the cytotoxic of the Ehrlich cells was scheduled as follows. The bottles were placed on their sides and the coverslip glasses closely fitted to the lower interior surfaces. The initial concentration of the Ehrlich cell suspension prepared for the experiment was 10 per cent/volume. This cell suspension was divided into 1 ml for each bottle. After being cultured stationary for 1 day at 37°C a monolayer of the cultured Ehrlich cells developed. Some of the bottles were exposed to 200 R and 3 hours later 0.1 ml of the complement solution and 0.1 ml of the anti-Ehrlich cell serum of the dd/YF mice or of the rabbits respectively were added to some of these exposed and unexposed bottles. The small pieces of coverslip glass with the mounted monolayered Ehrlich cells were taken out 15, 30, 45, 60 min, 2, 3, 4, 5 hrs and 1, 2 and 4 days respectively after being incubated with

cantly lower D_0 values than those for the original cells. Comparison between the radiosensitivities of normal and malignant cells yielded relatively small differences.

In order to make malignant cells more radiosensitive than benign cells, sensitization of the former to irradiation by oxygenation (GRAY et coll 1953) and chemical sensitizers (DJORDJEVIC & SZYBALSKI 1960, ERIKSON & SZYBALSKI 1961 and BERRY & ANDREWS 1962) has been undertaken.

Several investigations have demonstrated, however, that some inbred lines of animals may react immunologically against the syngenic tumors, since FOLEY (1953) reported on the antigenicity of methylcholanthrene induced sarcomas. Tumor specific immunization seems to be another method of modifying the apparent radiosensitivity of neoplasms (SCOTT 1961 and HADDOW 1961).

In the present experiments, the diffusion chamber technique was used, a sort of *in vivo* culture method, originating from PREHN et coll (1951) and reviewed by AMOS (1961). By this method the inoculated cells within the diffusion chamber are isolated from the host cells. The humoral factors may be transfused both ways, from outside to inside the diffusion chamber, and vice versa, and the number of cells can be counted after the scheduled culture *in vivo*, precisely as cells cultured *in vitro*. Also, a technique of immunologic cytolysis *in vitro* has been developed in order to investigate the interaction between radiologic and immunologic treatments as revealed in dose response curves for the Ehrlich cells on a cellular level, as well as to analyse the immunologic factor participating in suppressing the apparent Ehrlich cell growth.

Materials and Methods

Ehrlich murine ascites tumor cells. The cells (obtained from Prof. J. Sato of the Cancer Institute Okayama University Medical School) were maintained *in vitro*; they were registered with the Japan Tissue Culture Association as the J1C11 line.

In vitro culture method. The medium for the Ehrlich cell culture was prepared from a modified Hanks solution containing 64 g NaCl, 3.2 g KCl, 1.6 g $MgSO_4 \cdot 7H_2O$, 1.6 g CaCl₂, 0.18 g KH_2PO_4 , 0.48 g $Na_2HPO_4 \cdot 12H_2O$, 8.0 g glucose, 0.1 g phenol red and 1 000 ml H_2O and from an A solution containing 800 mg streptomycin sulfate, 504 mg penicillin G crystal and 1 000 ml H_2O .

These two solutions were prepared beforehand and stored in refrigerator (4°C) for the final mixing. The YLH solution (final mixture) contained 0.2 g yeast extract (Difco), 1.0 g lactalbumin hydrolyzate, 25 ml modified Hanks solution, 0.9 g glucose, 0.125 g $NaHCO_3$, 25 ml A solution, 150 ml H_2O . The YLH solution was filtered with Seitz's filtration apparatus. Inactivated calf serum (20 volume per cent) was added immediately before the final solution was utilized as *in vitro* culture medium.

The initial cell concentration of the suspension prepared for the *in vitro* dose response

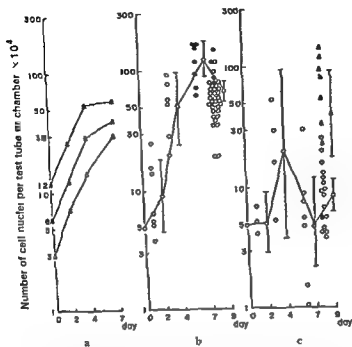


Fig 2. Control of growth experiments. a) *In vitro*. Three different initial numbers of cells were adopted. Each triangle, whether closed or open, represents average data from 5 to 10 culture test tubes. In trial number 3×10^4 / 5 ml/tube was selected to be used for *in vivo* dose response experiments and is indicated by open triangles. b) *In vivo*. Diffusion chambers and conventional dd/yF male mice were used, adopting the initial number 5×10^4 / 0.2 ml/chamber. Each circle, whether open or closed, represents data obtained from one host mouse (these data were obtained from several series using the same experimental procedures). Closed circles indicate those obtained from a single one of these series. c) *In vivo*. Diffusion chambers in dd/yF male mice immunized with either the Ehrlich cells or dd/yF mouse leukemia and the same initial number as for (b). Each open circle represents the data obtained from one host mouse immunized with the non-proliferative Ehrlich cells 3×10^4 in number, and each closed triangle indicates immunization with liver tissue of 0.4 g wet weight. Log mean values with 90% confidence intervals are given in (b) and (c).

After staining and microscopy, no Ehrlich cells could be observed on these coverslip glasses. The Ehrlich cells are distinguishable by being remarkably larger than host mouse cells. The cell count in the interior of the diffusion chambers revealed that no cells had penetrated the multipore filters in the chambers initially containing only culture medium, and in the Ehrlich cell chambers only Ehrlich cells were found. The chosen porosity, 0.22 μ of the

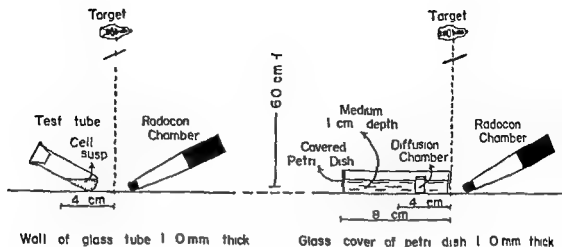


Fig. 1 Schematic drawing showing the arrangements for the irradiation procedure

the antiserum complement system. These coverslip glasses were then rinsed with physiologic salt solution warmed to 37°C, fixed with methanol and stained with Giemsa 1 day after the fixation and observed microscopically.

Irradiation procedure. The Ehrlich cell suspension was exposed to single doses of roentgen rays for the *in vitro* experiment in test tubes and for the *in vivo* experiment within the diffusion chambers immersed in YLH solution in covered Petri dishes (Fig. 1).

The physical factors of irradiation were 190 kV, 24 mA, 1.0 mm Cu and 0.5 mm Al filtration, 60 cm target-object distance, 37 R/min in air and room temperature. The roentgen rays were generated by Toshiba's X-ray apparatus KXC 18 2A. The doses were measured with Victoreen's Radocon Model 575 and Chamber Model 601.

Cell counting method. In all instances except for the cytotoxicity experiment, the Ehrlich cells after the scheduled incubations were stained by crystal violet in citric acid solution and the number of nuclei counted using the Buerker-Tuerk type of haemocytometer. The diffusion chamber containing the cultured cells was immersed in the staining solution; the millipore filters attached to both surfaces were broken with the tip of a pipette; the staining solution was pipetted and then the nuclei in the suspension were counted.

Statistical analysis. The data obtained in the dose-response experiments *in vivo* were analysed by logarithmic F distribution and the 95% confidence intervals were estimated.

Results

Migration of cultured and host cells through the millipore filters. After the implantation of the diffusion chamber for 9 days, the host mice were sacrificed, the abdominal wall was opened and the chambers removed. Coverslip glasses were mounted by pressing them against the peritoneal membranes of some of the host mice, in which chambers containing the Ehrlich cells had been implanted.

Table 3

Number of residual intact Ehrlich cell nuclei after immunologic cytotoxicity

Relative volume of antisera	Intact cell nuclei * ($\times 10$)							
	Anti Ehrlich cell mouse serum				Anti Ehrlich cell rabbit serum			
	Cases			Mean	Cases			Mean
10	55	59		57	13	16	18	16
1	67	67	86	72	36	42	46	41
0.1	58	134	141	111	47	71	77	63
0.01	94	95	103	97	98	116	130	115

Initial number of Ehrlich cell nuclei 10×10

Thus in the conventional hosts the control growth curves both in vitro and in vivo seemed to maintain approximately an exponential growth during the experimental period while the number of surviving cell nuclei of the 9 day culture varied according to the logarithmic normal distribution.

Dose responses The dose response curves are presented in Figs 3 and 4. The most remarkable characteristic in these curves is that the dose response curve in the hosts immunized against the Ehrlich cells is displaced downward to run approximately parallel to the curve in the conventional hosts. The experimental conditions, extrapolation numbers and 37% survival doses in the straight portions of the dose response curves as slopes (D_{01}) are given in Table 1. The upper two extrapolation numbers appear to be similar and the third one to be larger than the upper two while the differences in the 37% doses are probably insignificant.

Relationship of initial cell number and suppression rate by immunization Three different initial cell numbers 2.5×10^5 and 7.5×10^5 (0.2 ml) chamber were adopted for the in vivo culture within diffusion chambers for nine days in both the immunized and the control hosts. The non irradiated Ehrlich cells were contained in the diffusion chambers. Similar suppression rates by the immunization were obtained in the experimental series with each initial cell number by comparing the final cell numbers in the immunized with those in the control hosts (see Table 2).

Cytotoxicity experiments The Ehrlich cell nuclei in the control yielded a 2 fold increase of the initial cell number after the Ehrlich cell suspension had been incubated for 1 day without complement or antiserum. As shown in Table 3

Table 1

Extrapolation numbers and 37 ° survival doses in three series of experiments

Conditions		Extrapolation number	37 ° dose (slope)
Irradiation	Culture		
In vitro	In vitro	1.3	310 R
In vitro	In vivo in conventional hosts	1.4	275 R
In vitro	In vivo in immunized hosts	2.2	270 R

Table 2

Relationship of initial cell number and suppression rate by immunization

Initial cell number ($\times 10^4$)	Log suppression rate* with 95 % confidence interval
2.5	0.54 \pm 0.30
5	0.44 \pm 0.07
7.5	0.44 \pm 0.07

* Suppression rate =
$$\frac{\text{Relative log survival in the immunized hosts}}{\text{Relative log survival in the control hosts}}$$

millipore filter prevented cell migration, the critical porosity of 0.45 μ m² sometimes permit migration of small cells through the filter.

Control growth. All data for the control growth are given in Fig. 2. The number of cell nuclei in the control after 9 days produced a 1.3 fold increase in the initial cell number in the conventional hosts, an 8 fold increase in the hosts immunized against the isologous liver (closed triangles), but in the hosts immunized against the Ehrlich cells only a 1.7 fold increase (open circles).

In the control growth in vivo, in the hosts immunized against the Ehrlich cells, the number of cell nuclei in the 2, 4, 7 and 9 day cultures were not significantly different from the number of nuclei at the beginning of the culture (Fig. 2c). In the conventional hosts, the Ehrlich cells after 7 day culture showed a higher cell number than those after 9 days. The 9 day growth data, obtained from the same experimental series as for the control growth after 7 days, are shown with closed circles among all the 9 day controls. The growth rate in the control for 7 days in vitro (open triangles) gave a similar value to that in vivo for 9 days in the conventional hosts.

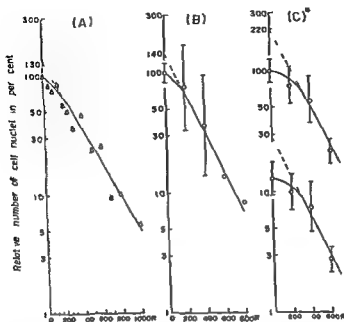


Fig 4 Dose response curves a) *In vitro* The values indicated by open triangles in fig 3a were shifted to values relative to the final number of non irradiated control growths for 7 days b) Relative log mean values with 95% confidence intervals were estimated from data given in fig 3b c) The upper curve represents the estimated log mean values with 95% confidence intervals relative to the final number of the non irradiated Ehrlich cell growths in the hosts immunized with Ehrlich cells The lower curve is the same as the upper curve except that it represents the estimated values relative to those in the conventional hosts

different periods with the inactivated anti Ehrlich cell rabbit or mouse serum and the complement solution The first damage was observed 15 min after incubation with the rabbit antiserum Longer incubation resulted in more distinct damage to the cytoplasmic portion of the cells

Microscopic observations at 15 min 2 and 4 hrs and at 4 days after incubation with the rabbit antiserum and complement are illustrated in Fig 5 Incubation with the complement solution and without the antiserum resulted in little cytoplasmic damage to the Ehrlich cells as shown in Fig 6 Fig 7 shows the observations 2 and 5 hrs after incubation with the mouse antiserum and complement The incubation of the previously irradiated Ehrlich cells with 200 R three hours before adding the mouse antiserum and complement did not result in any cytoplasmic damage greater than that in the non irradiated cells at 5 hrs after the antiserum and complement had been added

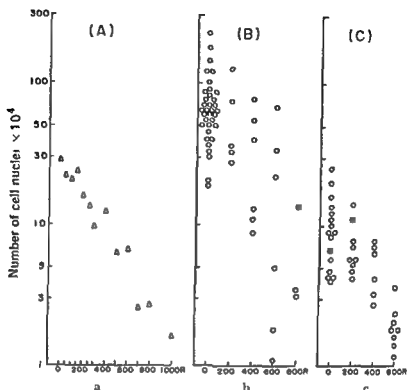


Fig. 3 Dose response curves a) *In vitro* Open triangles indicate average final number of Ehrlich cell nuclei after 7 day culture. Initial number was 3×10^4 /tubes. At beginning of culture the tubes containing the Ehrlich cell suspension were treated with several doses of roentgen irradiation b) *In vivo* Each open circle indicates data of culture for 9 days in diffusion chamber obtained from each of the conventional dd/Y male hosts. The Ehrlich cells $\times 10^4$ in initial number just before the implantation were treated in the diffusion chamber with several doses of roentgen irradiation c) Same as for (b) except that hosts immunized with 3×10^4 Ehrlich cells 10 days before the chamber implantation were used

the addition of irradiated anti Ehrlich cell mouse or rabbit sera resulted in cytolysis of the Ehrlich cells when the Ehrlich cell suspension was incubated for 1 day with one of these antisera together with the complement, while without complement the addition of these antisera did not seem to result in cytolysis of the Ehrlich cells, neither did the cell number increase when incubated. The number of Ehrlich cells not undergoing cytolysis was apt to increase with the decrease in relative volume of the anti Ehrlich cell sera. However, this tendency was much more apparent when the Ehrlich cells were incubated with the rabbit antiserum than with that of mice.

On the other hand, the morphologic damage of the Ehrlich cells by the antiserum was observed microscopically after they had been incubated for

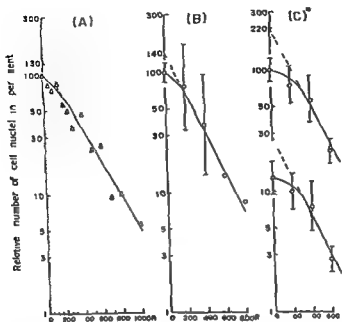


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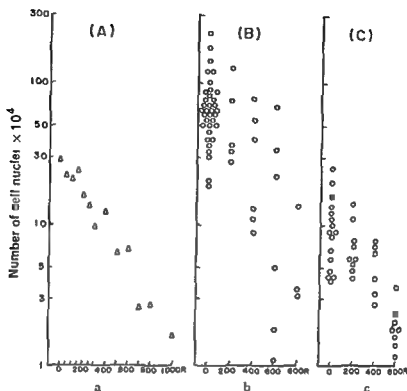


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On the other hand, the morphologic damage of the Ehrlich cells by the antiserum was observed microscopically after they had been incubated for



Fig 1 Cytolysis of Ehrlich cells. Giemsa $\times 600$ Microscopic observations at 1 hour (a) and 3 hours (b) after incubation with complement. The cytoplasm is intact.

no change in the number of cell nuclei after the 1 day incubation was observed and little cell debris was noted in either of the present experimental systems of cytolysis.

Discussion

Character of host resistance factor transfusible into diffusion chamber. Despite the cell impermeability of 0.22μ millipore filter as shown in the results and demonstrated by NETTESHEIM et coll (1966) the apparent Ehrlich cell growth within the diffusion chamber was suppressed when cultured in the host immunized against the Ehrlich cells as shown in Fig 2c. It was therefore considered that some humoral factor in the ascites fluid of the immunized host was transfusible into the diffusion chamber. After 9 day culture no significant difference was found between the numbers of the cell nuclei in the conventional hosts and in those immunized against the isologous liver (Fig 2b) whereas the difference in the number of cells between hosts immunized against the isologous liver and those immunized against the Ehrlich cells was significant (Fig 2c). Thus in the present *in vivo* experimental system the humoral factor in the immune ascites fluid seemed to be the immunologic reagent against the Ehrlich cells.

The prepared anti Ehrlich cell serum of dd/YF mice is considered to be an isoantiserum while that of rabbits is probably a heteroantiserum. When the Ehrlich cells were incubated without the complement neither antisera produced any major cytolysis of the Ehrlich cells. The higher the concentration of the antisera incubated with the complement the lower was the number of Ehrlich cells that apparently remained intact. Thus in the present *in vitro*

Fig. 3. Cytolysis of Ehrlich cells. Giemsa $\times 600$. Microscopic observations: a) Control (Ehrlich cells with sharply defined cytoplasm); b) at 15 min; c) at 2 hours; d) at 4 hours and e) 4 days after incubation with anti Ehrlich cell rabbit serum and complement. There is an obvious relationship between increase in intensity damage to cytoplasm and time after incubation.



Cytolysis was distinctly observed within a rather short period of incubation with the heteroantiserum complement system but was not noteworthy with the isoantiserum complement system. The damage to the cytoplasmic portion in these experiments was observed morphologically before the damage to the cytonucleic portion.

The mouse isoantiserum seems to be characteristic in suppressing the apparent Ehrlich cell growth rather than in producing any marked cytolysis, because



Fig 1 Cytolysis of Ehrlich cells (Giemsa $\times 600$) Microscopic observations at 2 hours (a) and 3 hours (b) after incubation with complement. The cytoplasm is intact.

no change in the number of cell nuclei after the 1 day incubation was observed and little cell debris was noted in either of the present experimental systems of cytolysis.

Discussion

Character of host resistance factor transfusible into diffusion chamber. Despite the cell impermeability of 0.22μ millipore filter as shown in the results and demonstrated by NETTESHEIM et coll (1966) the apparent Ehrlich cell growth within the diffusion chamber was suppressed when cultured in the host immunized against the Ehrlich cells as shown in Fig 2c. It was therefore considered that some humoral factor in the ascites fluid of the immunized host was transfusible into the diffusion chamber. After 9 day culture no significant difference was found between the numbers of the cell nuclei in the conventional hosts and in those immunized against the isologous liver (Fig 2b) whereas the difference in the number of cells between hosts immunized against the isologous liver and those immunized against the Ehrlich cells was significant (Fig 2c). Thus in the present *in vivo* experimental system the humoral factor in the immune ascites fluid seemed to be the immunologic reagent against the Ehrlich cells.

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Fig. 7. Cytolysis of Ehrlich cells (Ciemura $\times 600$). Microscopic observations at 2 hours (a) and 5 hours (b) after incubation with anti-Ehrlich cell ddY F mouse serum and complement. In (c) and (d) the Ehrlich cells were treated with 200 R at 3 hours before the incubation. There is less damage of cytoplasm as compared with fig. 6.

experimental system, the complement fixation reaction seemed to be the most probable mode of immunologic cytolysis. However, when the Ehrlich cells were incubated with much diluted anti-Ehrlich cell mouse serum, 0.01 volume per cent together with the complement, the apparent number of Ehrlich cells neither increased nor cytolytically decreased, as indicated in Table 3. With this concentration of the antiserum, two possibilities may explain the cell number kinetics: (1) the decrease in the cell number by cytolysis and its increase by proliferation were apparently neutralized by each other or (2) the Ehrlich cell proliferation was suppressed and the cytolysis was slight. The latter possibility is rather probable, because cells, damaged by cytolysis or cell debris were not distinctly observed microscopically after incubation with this concentration of antiserum. AMOS & WAKEFIELD (1958) have described an iso

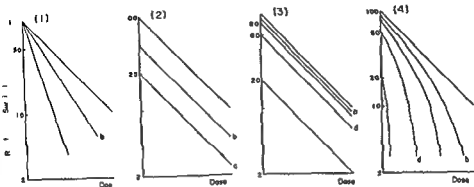


Fig 11 The four theoretical formulas and their curves

(1) represents $y = y_0 - k A_{imm} D$ For the respective curves A_{imm} is in (a) = 1 in (b) = 1.5 and in (c) = 3

(2) represents $y = y_0 B_{imm} e^{-k D}$ For the respective curves B_{imm} is in (a) = 1 in (b) = 0.5 and in (c) = 0.25

(3) $y = (y_0 - y_{imm}) e^{-k D}$ (a) $y_{imm} = 0$ (b) $y_{imm} = 0.1$ (c) $y_{imm} = 0.2$ (d) $y_{imm} = 0.4$ (e) $y_{imm} = 0.8$

(4) $y = y_0 e^{-k D - y_{imm}}$ (a) $y_{imm} = 0$ (b) $y_{imm} = 0.1$ (c) $y_{imm} = 0.2$ (d) $y_{imm} = 0.4$ (e) $y_{imm} = 0.8$

immune ascites fluid in which hemagglutinating neutralizing and protective effects were demonstrated. Cytotoxic effects of iso immune sera against a lymphoma cell line could be demonstrated with a variety of techniques both in vitro (GORER & O GORMAN 1956) and in vivo (GORER 1942 and GORER & AVOS 1956).

Control growth in vivo in immunized mice The number of cell nuclei in the hosts immunized against the Ehrlich cells did not change significantly during the 9 days of culture (Fig 2c). It was expected that the control growth curve would display a more or less moderate slope; the number of cell nuclei in the 4 day culture varied however and included cases that were as well proliferated as those in the conventional hosts. The most probable reason for the variation of the cell number in the 4 day culture is that until the transfusion of immune ascites fluid into the chamber has not been adequately established after the operative implantation of the chamber some of the apparent 4 day growths are not quite suppressed by the immunization. This explanation would be in accord with the data of the cytotoxic experiments in vitro in which the Ehrlich cells were adequately exposed to the antiserum and complement the cytoplasmic portion then being damaged and the apparent growth suppressed within one day.

Possible theoretical dose response formulas under the cooperative condition between irradiation and immunization The results obtained seem to indicate that irradiation and immunization suppress the apparent Ehrlich cell growth, simultaneously but probably in different manners. Theoretical formulas for this joint action are proposed in the following (Fig. 8)

- (1) $N = N_0 e^{-K A_{imm} D}$, (2) $N = N_0 B_{imm} e^{-K D}$, (3) $N = (N_0 - N_{imm}) e^{-K D}$,
 (4) $N = N_0 e^{-K D} - N_{imm}$

where

N surviving cell number

N_0 initial cell number

N_{imm} number of cells destroyed by immunological reaction

K cell intrinsic radiosensitivity coefficient

A_{imm} and B_{imm} the coefficients by which immunological reaction modifies these formulas, and

D the irradiation dose

These formulas are applicable unmodified, when cell proliferation kinetics can be excluded experimentally, as with the colony formation method. When cell proliferation kinetics are included, as in a cell counting method, N_0 should be multiplied by the growth rate, a function of the irradiated dose, if the growth rate is dose dependent. However, as observed in the present cytotoxic experiments, incubation with the iso antiserum suppressed the cell growth. Among the groups of cells, which were irradiated with various doses and cultured either in the immunized or in the conventional hosts, the postulation of a non-proliferating cell system or equivalent growth rates may explain these theoretical formulas simply as follows.

In formula (1), A_{imm} modifies the original coefficient K , to the apparent coefficient $K \times A_{imm}$. When A_{imm} is larger than 1, cells are sensitized by the immunization, when A_{imm} is smaller than 1, cells are protected from irradiation by the immunization, and when $A_{imm} = 1$, the immunization has no effect on the apparent radiosensitivity. When cells are not irradiated, the existence of immunization in this mode has no effect. It may be so weak that the apparent cell growth may not be damaged by the immunization alone. The ratio inactivation to intensity of immunization is constant within a certain range, regardless of the initial cell number N_0 , as seen in Fig. 9—(1).

In formula (2), the immunization multiplies the initial cell number by the coefficient B_{imm} . When B_{imm} is smaller than 1, N_0 is reduced. In this mode, the ratio inactivation to intensity of immunization is constant within a certain range regardless of the initial cell number N_0 , as shown in Fig. 9—(2).

In formula (3), N_0 is directly reduced by N_{imm} , and the intact cells, i.e. $(N_0 - N_{imm})$, are damaged by irradiation. N_{imm} in this mode for $N_0 >$

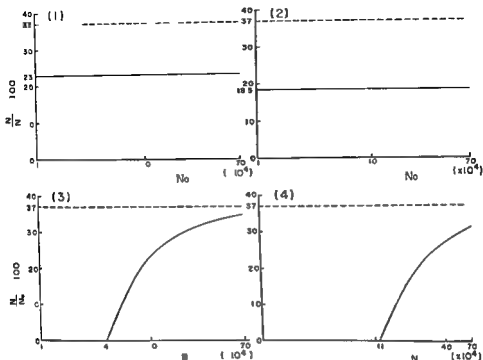


Fig 9 Relationship between N and N/N_0 in the four theoretical formulas shown in fig 8

- (1) When A_{imm} is 1.5 and the cells were treated in vitro with the original 37 dose in vivo, $N/N_0 = 100$ is constant regardless of the variety of the initial number N_0 according to theoretical formula (1).
- (2) When B_{imm} is 0.5 and the cells are treated with $D = N/N_0 \times 100$ is also constant regardless of the variety of the initial number N_0 according to theoretical formula (2).
- (3) When $N_{imm} = 4 > 10$ and constant according to the intensity of the immunization but not relative to N_0 and the cells are treated with $D = N/N_0 \times 100$ is as the curve in fig 9 (3) according to theoretical formula (3).
- (4) When conditions are the same as in (3) the curve in fig 9 (4) is according to theoretical formula (4).

N_{imm} is independent of the initial number N_0 within a certain range but dependent on the intensity of the immunization. However, N/N_0 varies according to the variation of N as shown in Fig 9—(3).

In formula (4) N_{imm} is reduced from the survivals after irradiation, i.e. $(N \times e^{-\lambda D})/N_0$ varies according to the variation of N_0 as shown in Fig 9—(4).

Among these four formulas, formula (2) and formula (3) generate inactivation curves similar to those obtained in the present experiments with the immunized hosts. Formula (3) may be neglected because the initial number of Ehrlich cells 2.5×10^6 for one immunized mouse manifested well proliferated

Possible theoretical dose response formulas under the cooperative condition between irradiation and immunization The results obtained seem to indicate that irradiation and immunization suppress the apparent Ehrlich cell growth, simultaneously but probably in different manners. Theoretical formulas for this joint action are proposed in the following (Fig. 8)

$$(1) N = N_0 e^{-k A_{\text{imm}} D}, \quad (2) N = N_0 B_{\text{imm}} e^{-k D}, \quad (3) N = (N_0 - N_{\text{imm}}) e^{-k D},$$

$$(4) N = N_0 e^{-k D} - N_{\text{imm}}$$

where

N surviving cell number

N_0 initial cell number

N_{imm} number of cells destroyed by immunological reaction

k cell intrinsic radiosensitivity coefficient

A_{imm} and B_{imm} the coefficients by which immunological reaction modifies these formulas, and

D the irradiation dose

These formulas are applicable unmodified, when cell proliferation kinetics can be excluded experimentally, as with the colony formation method. When cell proliferation kinetics are included, as in a cell counting method, N_0 should be multiplied by the growth rate, a function of the irradiated dose, if the growth rate is dose dependent. However, as observed in the present cytotoxic experiments, incubation with the iso-antiserum suppressed the cell growth. Among the groups of cells, which were irradiated with various doses and cultured either in the immunized or in the conventional hosts, the postulation of a non-proliferating cell system or equivalent growth rates may explain these theoretical formulas simply as follows.

In formula (1), A_{imm} modifies the original coefficient k to the apparent coefficient $k \times A_{\text{imm}}$. When A_{imm} is larger than 1, cells are sensitized by the immunization, when A_{imm} is smaller than 1, cells are protected from irradiation by the immunization, and when A_{imm} is = 1 the immunization has no effect on the apparent radiosensitivity. When cells are not irradiated, the existence of immunization in this mode has no effect, it may be so weak that the apparent cell growth may not be damaged by the immunization alone. The ratio inactivation to intensity of immunization is constant within a certain range, regardless of the initial cell number N_0 , as seen in Fig. 9—(1).

In formula (2), the immunization multiplies the initial cell number by the coefficient B_{imm} . When B_{imm} is smaller than 1, N_0 is reduced. In this mode, the ratio inactivation to intensity of immunization is constant within a certain range regardless of the initial cell number N_0 , as shown in Fig. 9—(2).

In formula (3), N_0 is directly reduced by N_{imm} and the intact cells, i.e. $(N_0 - N_{\text{imm}})$, are then damaged by irradiation. N_{imm} in this mode, for $N_0 >$

modified by adding a factor P which is a function of the suppression coefficient for growth rate by the immunization as follows

$$2^{P_{imm}}/2^{P_0} = 2^P = e^{-Q}$$

where P_0 and P_{imm} = the number of cell divisions estimated in the apparent Ehrlich cell number in the conventional and immunized hosts respectively, in which it is assumed that the cells proliferated homogeneously

$$\begin{aligned} \lambda &= \lambda_0 e^{-\lambda A_{imm} D} e^{-Q} \\ &= \lambda_0 e^{-\lambda A_{imm} (D + Q/\lambda)} = \lambda_0 e^{-\lambda A_{imm} D} \end{aligned} \quad (1)$$

$$\begin{aligned} \text{where } D &= D + Q/\lambda A_{imm} \\ \lambda &= \lambda_0 B_{imm} e^{-K(D + Q/\lambda)} = \lambda_0 B_{imm} e^{-\lambda D} \end{aligned} \quad (2)$$

$$\begin{aligned} \text{where } D &= D + Q/\lambda \\ \lambda &= (\lambda_0 - \lambda_{imm}) e^{-\lambda D} \end{aligned} \quad (3)$$

$$\lambda = \lambda_0 e^{-\lambda D} - \lambda_{imm} \quad (4)$$

Thus these four further modified formulas gave curves which were shifted parallel from right to left on the semilog diagrams shown in Fig 10 representing c to c (1) b to b (2) d to d (3) and e to e (4)

Immunization may sometimes modify the dose response curve by either one of these formulas or in other instances by some of them in the mixed mode Furthermore, the extent to which the formulas are simultaneously relevant may vary in every case Assuming that one of these four formulas interprets the main mode of the modification the data obtained in the present experiments seem to be in accordance with formula (2) or formula (4)

In the present series of experiments the homograft immunization may be considered stronger than possible against autologous tumors Cellular factors could be neglected since the assay of the Ehrlich cell kinetics *in vivo* could be undertaken with the diffusion chamber

SCIT & SHALEA (1963) have suggested that an estimated 37 % dose D_0 would be smaller than the true D_0 of a tumor cell line In this case the tumor cells were cultured in the syngenic hosts to the tumor which had been repeatedly injected with the killed tumor cells In this case the experimental system consisted of a spontaneous mammary adenocarcinoma and syngenic hosts in which weak immunization might exist were adopted cellular factors being included This data may be related to formula (1)

HADDOW (1964) has reported that the effect of a tumor specific immunization for suppressing the increase of the syngenic tumor volume was observed only in the irradiated group of tumors but not in the non irradiated control

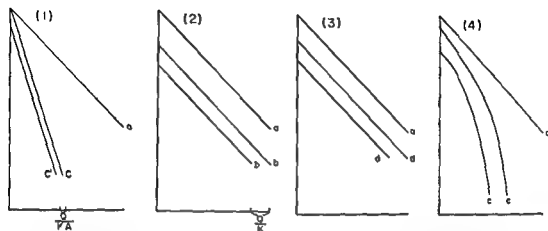


Fig. 10 Further modified theoretical formulas and their curves. These further modified curves were obtained with parallel shift from the right to the left side on semilog section paper.

$$(1) (a) \lambda = \lambda_0 e^{-\lambda A_{imm} D}$$

$$\text{where } A_{imm} = 1$$

$$(c) \lambda = \lambda_0 e^{-\lambda A_{imm} D}$$

$$\text{where } A_{imm} = 3$$

$$(c) \lambda = \lambda_0 e^{-\lambda A_{imm} D}$$

$$\text{where } A_{imm} = 3$$

$$D \approx D + Q/\lambda$$

$$(2) (a) \lambda = \lambda_0 B_{imm} e^{-\lambda D}$$

$$\text{where } B_{imm} = 1$$

$$(b) \lambda = \lambda_0 B_{imm} e^{-\lambda D}$$

$$\text{where } B_{imm} = 0.5$$

$$(b) \lambda = \lambda_0 B_{imm} e^{-\lambda D}$$

$$\text{where } B_{imm} = 0.5$$

$$D \approx D + Q/\lambda$$

$$(3) (a) \lambda = (\lambda_0 - \lambda_{imm}) e^{-\lambda D}$$

$$\text{where } \lambda_{imm} = 0$$

$$(d) \lambda = (\lambda_0 - \lambda_{imm}) e^{-\lambda D}$$

$$\text{where } \lambda_{imm} = 0.4 \quad \lambda_0$$

$$(d) \lambda = (\lambda_0 - \lambda_{imm}) e^{-\lambda D}$$

$$\text{where } \lambda_{imm} = 0.4 \quad \lambda_0$$

$$D \approx D + Q/\lambda$$

$$(4) (a) \lambda = \lambda_0 e^{-\lambda D - \lambda_{imm}}$$

$$\text{where } \lambda_{imm} = 0$$

$$(c) \lambda = \lambda_0 e^{-\lambda D - \lambda_{imm}}$$

$$\text{where } \lambda_{imm} = 0.2 \quad \lambda_0$$

$$(c) \lambda = \lambda_0 e^{-\lambda D - \lambda_{imm}}$$

$$\text{where } \lambda_{imm} = 0.2 \quad \lambda_0$$

$$D \approx D + Q/\lambda$$

growth, in spite of the fact that λ_{imm} had to be $5 \times 10^4 \times (1-0.13)$, i.e. 4.4×10^4 in the present experimental system.

However, the control growth in the immunized hosts did not show a sharp initial drop but rather non significant changes in the cell numbers during the *in vivo* culture period, especially after 4 days and the cytolysis experiment *in vitro* using the iso antiserum mainly suggested an apparent suppression of cell proliferation. Therefore, these four theoretical formulas should be further

crease in cell number is delayed or the growth rate decreases. On the other hand in the immunologically treated cells, the morphologic disorder is mainly observed in the cytoplasmic portion which is followed by morphologic desolation in the cell nuclei portion.

Thus the two different procedures both irradiation and immunization may co operate to damage the cells by attacking different portions in each cell the effects of which may appear in different manner and be mutually multiplied independently or even synergetically. The dose response curve in the *in vivo* experiment with immunized hosts manifested on semilog section paper an approximately parallel downward shift from that of conventional hosts which means multiplication of the damage by the two procedures. However, further damage such as the so-called sensitization effect to irradiation by immunization was not observed. The sensitization effect should be further investigated *in vitro* by adopting the diluted concentration of antibody (around 0.01 volume per cent).

Acknowledgement

The author wishes to thank Prof. T. Sugahara, Doctors Y. Ueno, M. Horikawa, Y. Daida and A. Vacek of the Department of Experimental Radiology and Y. Hamashima of the Department of Pathology, Faculty of Medicine, Kyoto University for their encouragement and advice in carrying out the present experiments. The author also wishes to thank Mr. T. Tanaka, Miss A. Onohara, Miss C. Sugiura, Miss A. Tsuboi and the other laboratory technicians for their technical assistance. His gratitude is also extended to Prof. J. Sato of the Cancer Institute, Okayama University Medical School for his courtesy in supplying the original Ehrlich cells. This work has been partially supported by a grant from Suntory Ltd.

SUMMARY

Iso-immune ascitic fluid was found to suppress Ehrlich cell growth in a diffusion chamber *in vivo*. The dose response curve in immunized hosts was displaced downwards to be parallel to that of conventional hosts. Application of the iso-immune serum against the Ehrlich cells resulted in their cytotoxicity when incubated *in vitro* with a complement solution. The possibility of the immunologic aspects contributing to the radiobiologic aspects of carcinoma therapy is discussed.

ZUSAMMENFASSUNG

Es konnte gezeigt werden, dass iso-immune Ascitesflüssigkeit das Wachstum von Ehrlichzellen in einer Diffusionskammer unterdrückt. In immunisierten Individuen war die dosisbedingte Reaktionskurve herabgedrückt und verlief parallel zu der von nicht immunisierten Individuen. Die Verabreichung von iso-immunem Serum gegen die Ehrlichzellen führte zu deren Cytolyse, wenn sie *in vitro* mit Komplementflüssigkeit inkubiert wurden. Es besteht demnach die Möglichkeit, dass immunologische Faktoren zu den radiobiologischen Wirkungen der Röntgenbestrahlung beitragen.

group. The dose response curve was not shown but formulas (1) or (4) would probably explain this data. Formula (4) gives the most theoretically effective inactivation curve for the purpose of cancer therapy. In any case in which a weak immunization exists, formulas (1) or (4) may not easily be distinguished by their dose response curves when some sensitization by the immunization occurs.

Experimental systems used by HADDOW and SUIT may include the cellular factors in the immunologic reactions, and the data suggest that formula (1) or (4) should be selected. On the other hand, in the present experimental system the cellular factors were excluded but the humoral factors were included and formula (2) was suggested. It is therefore probable that the humoral factor and the cellular factor in the immunologic reactions modify the dose response relationship in different manners.

Cellular aspect of radiation therapy in relation to immunology of cancer. The immunology of cancer has passed through three distinct periods as stressed by PREHN (1963). In the first of these, it was demonstrated that experimental animals could be immunized against the growth of transplanted tumors. In the second, it was clarified that the previous demonstration had been mainly due to homograft immunity. Finally, in the third it was demonstrated that in some isologously transplanted tumors, the growth could be suppressed in the immunized isologous hosts. Further, since the tumor specific antigenicities in some human malignancies have been recognized (KLEIN et coll 1966), cancer immunology has become one of the most important aspects of human cancer therapy (CINADINI 1963). After changes in cell character have taken place, both autonomous growth and tumor specific antigenicity may be possessed by some of the malignancies. If these two processes can exist simultaneously, all such malignancies may possess the tumor specific antigenicity, and if they can exist independently, some of the malignancies may theoretically possess the tumor specific antigenicity whereas others may not (BURCH 1963). The immunization may in the course of tumor therapy cause added damage to a tumor associated with the tumor specific antigenicity. Accordingly, in such cases the immunization may modify the dose response relationship, as stressed by SCOTT (1961).

Probably, some of the dose response relationships investigated *in vivo* and reported upon may have been modified by weak immunization, even if no immunological procedure was employed.

Morphological disorder in the irradiated cells is probably observed in the cell nuclei portion primary to morphologic desolation in the cytoplasmic portion. Giant cells associated with evident cytoplasm may appear, and in

- KLEIN ■ CLIFFORD P KLEIN EVA and STJERNQVARD J Search for tumor specific immune reactions in Burkitt lymphoma patients by the membrane immunofluorescence reaction Proc nat Acad Sci 55 (1966) 1628
- NETTESHEIM P MAKINODAN T and CHADWICK C J Improved diffusion chamber cultures for cytokinetic analysis of antibody response Immunology 11 (1966) 427
- PREHN R T WEAVER J M and ALGIRE G H The diffusion chamber technique applied to a study of the nature of homograft resistance J nat Cancer Inst 15 (1954) 509
- PLOCK T T and MARCUS P J Action of X rays on single mammalian cells J exp Med 103 (1956) 653
- SCOTT ■ C A Some observations on the use of transplanted tumors in radiobiological research Radiat Res 14 (1961) 643
- SUIT H D and SHALEK R T Response of spontaneous mammary carcinoma of the C3H mouse to X irradiation given under conditions of local tissue anoxia J nat Cancer Inst 31 (1963) 497
- WHITMORE G F and TILL J E Quantitation of cellular radiobiological responses Ann Rev nuclear Sci 14 (1964) 347
- WILLIAMS J T and TILL J E The radiation sensitivity of normal and polyoma transformed rat embryo cells Radiat Res 29 (1966) 287

RÉSUMÉ

L'auteur a constaté que le liquide d'ascite iso-immun supprime la croissance des cellules d'Ehrlich dans une chambre à diffusion *in vivo*. La courbe de réponse en fonction de la dose chez les hôtes immunisés est déplacée vers le bas et située parallèlement à celle des hôtes non immunisés. L'incubation *in vitro* de cellules d'Ehrlich avec une solution de complément et application de sérum iso-immun entraîne leur cytolysse. L'auteur examine la possibilité d'une coopération de l'immunologie et de la radiobiologie au traitement du cancer.

REFERENCES

- AMOS D. B.: *Transplantation of cells and tissue in diffusion chamber* In *Transplantation of tissues and cells* p. 69. Edit. by E. E. Billingham and W. K. Silvers. Wistar Institute Press Philadelphia 1961.
- and WAKEFIELD J. D.: Growth of mouse ascites tumor cells in diffusion chambers. I. Studies of growth rate of cells and of the rate of entry of antibody. *J. Nat. Cancer Inst.* 21 (1958) 657.
- BERRY R. J. and ANDREWS J. R.: Modification of the radiation effect on the reproductive capacity of tumor cells *in vivo* with pharmacological agents. *Radiat. Res.* 16 (1962) 82.
- BURCH P. R. J.: Carcinogenesis and cancer prevention. *Nature* 197 (1963) 1145.
- CINADER B.: Perspectives and prospects of immunotherapy. Autoantibodies and acquired immunological tolerance. *Canadian Cancer Conference Honey Harbour* 5 (1963) 279.
- DJORDJEVIC B. and SZYBALSKI W.: Genetics of human cell lines. III. Incorporation of 3-bromo- and 5-iododeoxyuridine into the deoxyribonucleic acid of human cells and its effects on radiation sensitivity. *J. exp. Med.* 112 (1960) 509.
- ERIKSON R. L. and SZYBALSKI W.: Molecular radiobiology of human cell lines. I. Comparative sensitivity to X-rays and ultraviolet light of cells containing halogen substituted DNA. *Biochem. biophys. Res. Comm.* 4 (1961) 258.
- FOLEY E. J.: Antigenic properties of methylcholanthrene induced tumors in mice of the strain of origine. *Cancer Res.* 13 (1953) 835.
- GORER P. A.: The role of antibodies in immunity to transplanted leukaemia in mice. *J. Path. Bact.* 54 (1942) 51.
- and AMOS D. B.: Passive immunity in mice against C57BL leukemia. E. L. 4 by means of iso immune serum. *Cancer Res.* 16 (1956) 338.
- and O'GORMAN P.: The cytotoxic activity of isoantibodies in mice. *Transplant. Bull.* 3 (1956) 142.
- GRAY L. H., CONGER A. D. and FIBERT M. et coll.: The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. *Brit. J. Radiol.* 26 (1953) 638.
- HADDOW A.: An immunological method of increasing the sensitivity of primary sarcomas to local irradiation with X-rays. *Lancet* 1 (1964) 452.
- HEWITT H. B. and WILSON C. W.: The effect of tissue oxygen tension on the radiosensitivity of leukaemia cells irradiated *in situ* in the livers of leukaemic mice. *Brit. J. Cancer* 13 (1959) 675.
- KANO E.: Comparative investigation on radiobiological responses of murine Ehrlich ascites tumor cells *in vitro* and *in vivo*. *Nippon Acta radiol.* 25 (1965) 1007.
- Analysis of a co-operative action of irradiation and immunological treatment against a malignant homograft. *Proc. Intern. Conf. Radiation Biology & Cancer* pp. 31–37. Kyoto 1966.

expression for it this expression is required for treatment planning with the use of computers

Measurement method The measurements were made with the Gammatron 1 cobalt 60 unit at the Radiotherapy Clinic the unit is equipped with block diaphragms

A Simplex Universal Dosimeter was employed for determination of the doses The radiation was detected with a normal ionization chamber made by the same manufacturer The chamber was encased in perspex to achieve electron equilibrium

Measurements were effected in a water phantom measuring 42 cm \times 36 cm \times 52 cm with perspex walls Cork material of density 0.27 g/cm³ was utilized as pulmonary tissue equivalent material Flat pieces of the cork material 0.3 to 0.6 cm thick, were placed in a thin walled perspex holder, and a lung phantom was thus obtained The phantom could be changed in position for measurement of the tissue effect at different locations The ionization chamber was situated in one of the pieces of cork By re arrangement of the pieces the position of the chamber could be changed for measurements at different depths in the cork material Four thicknesses of the lung phantom were used 3.1, 6.3, 9.4 and 12.5 cm the SSD (source to skin distance) was 50 cm

Results of measurements

The maximum dose in cobalt teletherapy is obtained at 0.5 cm below the surface this is assigned as the 100 % dose All other doses are compared with the maximum dose and are termed per cent depth doses

The central axis depth dose curve Straight lines are obtained when the logarithms of the per cent depth doses are plotted as functions of the depth below the surface (JONES et coll 1956 PFALZNER 1960) STERLING et coll (1964) have shown the possibility of expressing the per cent depth doses at the central axis as a function of the area per perimeter of the field According to their findings the following formula is valid

$$\log C_t = h_t + m_t \log (A/P) \quad (1)$$

where C_t is the per cent depth dose on the central axis of the field at a distance D_t (cm) from the surface

A/P is the ratio of the field area (cm²) over field perimeter (cm)

h_t and m_t are the intercept and slope constants respectively

EMPIRICAL FORMULAS FOR TISSUE CORRECTION FACTORS IN COBALT TELETHERAPY

by

LRIK SPRING and PENTTI ANTILA

Air filled lung tissue has an absorbing capacity which is considerably lower than that of the other soft tissues of the thorax. Consequently, any change in the radiation scattering conditions will greatly affect the dose distribution. The dose in the lung and behind it increases. This is important for the treatment planning, when such influence to the greatest extent possible must be taken into account.

Dose distributions are usually determined in a tissue equivalent medium, generally water. The change in distribution within and behind an inhomogeneity is observed and given due consideration in the treatment planning by means of tissue correction factors. The dose in the inhomogeneous region is arrived at by multiplication of the dose obtained in a homogeneous medium with the correction factor.

Tissue correction factors may be determined in several ways. One way is to compare the incident and exit doses determined for a patient with measurements performed with a tissue equivalent phantom (FRALZNER 1958, JOHNS 1964). Measurements effected in a tissue equivalent phantom (BURLIN 1957, DAHL and VIKTERLOF 1960, SUNDBOM 1965) or in the oesophagus (VOUTI, LAINEN & VAHATALO 1966) are also used. A tissue equivalent phantom has been employed in this study.

The aim of this work was to study the influence of pulmonary tissue upon the central axis depth dose curve with a view to finding a simple mathematical

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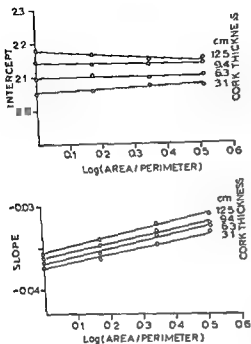


Fig. 3 Intercept and slopes of the straight lines adapted to the experimental values measured behind the cork phantom. Some of the results are given in figs 4 and 5.

dose curve within the lung can approximately be described by one formula. If the logarithm of the measured doses as a percentage of the depth dose value in the normal tissue at the boundary of the pulmonary tissue is plotted as a function of $\log(A/P)$ straight lines result. The experimental values together with the straight lines are presented in Fig. 2. If the slopes and the intercepts of the lines are plotted as functions of the depth in the pulmonary tissue approximately straight lines are obtained. The per cent depth dose in the pulmonary tissue may be expressed by the formula

$$C_t = (k_t/100) C_n \quad (3)$$

where

C is the normal tissue per cent depth dose at the entrance boundary between the normal tissue and the pulmonary tissue. It can be calculated by formula (2)

$$k_t = \text{antilog}[-0.024 D_t + (0.004 D_t - 0.008) \log(A/P) + 1.980]$$

D_t is the depth in the pulmonary tissue measured in cm

Figs 4 and 5 indicate the closeness of fit between the experimental points and the lines obtained by means of formula (3). The depth doses re

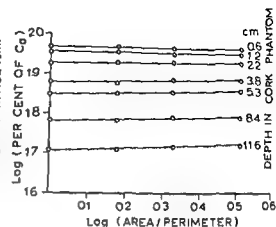
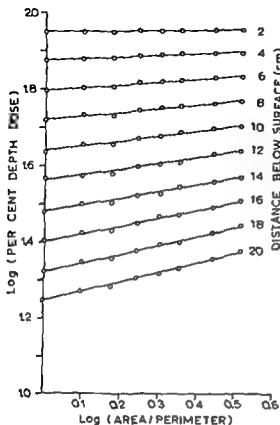


Fig 1 (left) Change in the central axis depth dose as a function of log (area/perimeter) of the field at 50 cm SSD

Fig 2 (above) Change in the central axis depth dose within the pulmonary tissue equivalent cork phantom. C_0 denotes the dose in water at the entrance boundary between water and cork

Use has been made of formula (1) in study of the central axis depth dose curve. Fig 1 illustrates the results of measurements and the straight lines determined by the method of least squares. It is apparent that close agreement exists between the experimental points and the straight lines. These provide a basis for determination of the constants h_i and m_i . $h_i = -0.039 D_i + 2.033$ and $m_i = 0.013 D_i + 0.006$.

Finally, the value of C_i , the per cent depth dose on the central axis at a distance D_i (cm) below the surface, is derived from the formula

$$C_i = \text{antilog}[-0.039 D_i + (0.013 D_i + 0.006)\log(A/P) + 2.033] \quad (2)$$

This formula describes very well the central axis depth dose curve, as is evident from Figs 4 and 5. An additional check of formula (1) was made by measuring the dose at different depths below the surface and a constant value of (A/P) but by introducing variation in the length of sides of the field. The results were found to lie within 1%.

Measurements within the inhomogeneity. The measurements in lung equivalent tissue were made with the cork phantom described. It was found that the depth

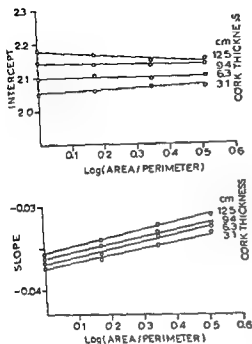


Fig 3 Intercepts and slopes of the straight lines adapted to the experimental values measured behind the cork phantom. Some of the results are given in figs 4 and 5.

dose curve within the lung can approximately be described by one formula. If the logarithm of the measured doses as a percentage of the depth dose value in the normal tissue at the boundary of the pulmonary tissue is plotted as a function of $\log(A/P)$ straight lines result. The experimental values together with the straight lines are presented in Fig 2. If the slopes and the intercepts of the lines are plotted as functions of the depth in the pulmonary tissue approximately straight lines are obtained. The per cent depth dose in the pulmonary tissue may be expressed by the formula

$$C_t = (k_t/100) C_a \quad (3)$$

where

C_a is the normal tissue per cent depth dose at the entrance boundary between the normal tissue and the pulmonary tissue. It can be calculated by formula (2)

$$k_t = \text{antilog}[-0.024 D_t + (0.004 D_t - 0.008) \log(A/P) + 1.980]$$

D_t is the depth in the pulmonary tissue measured in cm

Figs 4 and 5 indicate the closeness of fit between the experimental points and the lines obtained by means of formula (3). The depth doses re

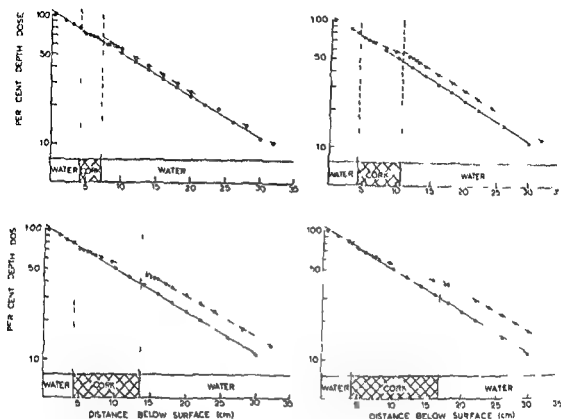


Fig. 4. Experimental results of measurements with SSB, 50 cm field 13 cm \times 13 cm and different thicknesses of the cork phantom ($\rho = 0.27$ g/cm³):
 ● measurements in water
 ○ measurements within and behind the cork phantom
 — calculated by formula (2)
 - - - calculated by formula (3) and (4)

remained constant for constant values of (A/P) , even within the cork phantom. The deviations in measurement lay within 1%.

Measurements behind the inhomogeneity. Finally, measurement was made of the depth doses beyond the pulmonary tissue, in the water behind the cork material.

Some of the derived experimental values are reproduced in Figs 1 and 2. First, by application of the method of least squares, straight lines were adapted to the experimental points, taken as the logarithms of the per cent depth doses. The intercepts and slopes obtained for these lines are given in Fig. 3 as functions of $\log(A/P)$. Plotting the intercepts and slopes as functions of the cork thickness will permit the adaptation of straight lines to the points concerned. Thus, formulae are obtained for the calculation of these para-

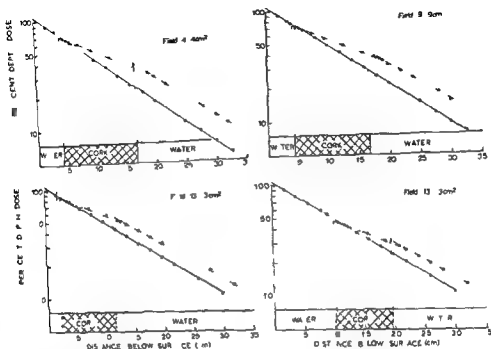


Fig. 5. Results similar to those in fig. 4 for SSD = 50 cm and fields 4 cm × 4 cm, 9 cm × 9 cm and field 13 cm × 13 cm and the cork phantom at two different depths below the surface.

● measurement in water
 — measurements within and behind the cork phantom
 — calculated by formula (2)
 — calculated by formulas (3) and (4)

meters for different cork thicknesses. In all the per cent depth doses behind the pulmonary tissue can be determined with the help of the following formula:

$$C_t = \text{antilog}\{[(0.0001 d_t + 0.0081)\log(A/P) + 0.0002 d_t - 0.0382]D_t + (-0.0103 d_t + 0.0703)\log(A/P) + 0.0132 d_t + 2.0151\} \quad (4)$$

where C_t is the per cent depth dose at the central axis at a depth D_t (cm) below the skin

d_t (cm) is the thickness of the pulmonary tissue

The other parameters have been defined earlier. The calculated results are compared with the experiments in Figs 4 and 5. The depth dose was measured behind the cork material keeping the ratio (A/P) constant and varying the field sizes. The results obtained were within 1%.

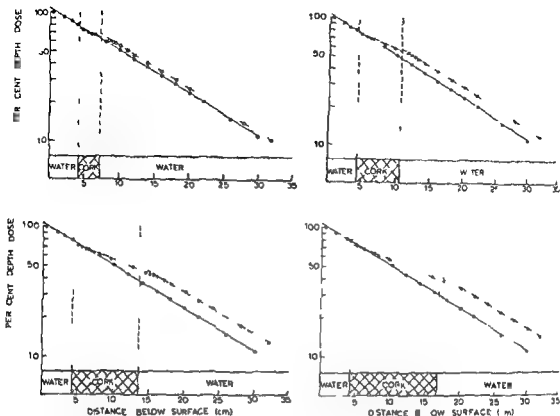


Fig 4 Experimental results of measurements with SSD = 50 cm, field 13 cm x 13 cm, and different thicknesses of the cork phantom ($\rho = 0.27 \text{ g/cm}^3$)

- measurements in water
- measurements within and behind the cork phantom
- calculated by formula (2)
- - - calculated by formula (3) and (4)

remained constant for constant values of (A/P) , even within the cork phantom. The deviations in measurement lay within 1%.

Measurements behind the inhomogeneity. Finally, measurement was made of the depth doses beyond the pulmonary tissue, in the water behind the cork material.

Some of the derived experimental values are reproduced in Figs 4 and 5. First, by application of the method of least squares, straight lines were adapted to the experimental points, taken as the logarithms of the per cent depth doses. The intercepts and slopes obtained for these lines are given in Fig 3 as functions of $\log(A/P)$. Plotting the intercepts and slopes as functions of the cork thickness will permit the adaptation of straight lines to the points concerned. Thus, formulas are obtained for the calculation of these para-

Acknowledgement

The authors wish to thank Mr S. Verho for his assistance in this study

SUMMARY

A study was performed with the aim of finding simple mathematical expressions for the per cent depth doses when pulmonary tissues are included. Three formulas are presented that fulfil the requirements for application in treatment planning using computers.

ZUSAMMENFASSUNG

Einfache mathematische Formeln um die prozentualen Tiefendosen zu bestimmen wenn die Bestrahlung auch Lungengewebe inkludiert wurden studiert. Als Resultat werden drei Formeln präsentiert und diese genügen um einen Bestrahlungsplan mit Hilfe einer Datenverarbeitungsmaschine aufzustellen.

RÉSUMÉ

Les auteurs ont cherché une expression mathématique simple du pourcentage de dose en profondeur quand le volume irradié comprend du tissu pulmonaire. Les résultats obtenus sont présentés sous forme de trois plans de traitement pour ordinateur.

REFERENCES

- BURLIN T. E. The evaluation of the dose to the thorax in rotational cobalt 60 therapy. *Brit. J. Radiol.* 30 (1957) 543.
- DAHL O. and VIKTERLOF K. J. Attainment and value of precision in deep radiotherapy. *Acta radiol.* (1960) Suppl. No. 189.
- JOHNS H. E. The physics of radiology. Second edition. Charles C. Thomas, Springfield, Illinois, 1964.
- JONES D. E. A., GREGORY C. and BIRCHALL I. Dosage distribution in rotational cobalt 60 therapy. *Brit. J. Radiol.* 29 (1956) 196.
- PFALZNER P. M. Transit-dose measurements in cobalt-60 rotation therapy dosimetry. *Radiology* 70 (1958) 503.
- A general formula for axial depth dose derived from an empirical power law for tumour air at om. *Radiology* 75 (1960) 438.
- ST. ORO L. Dose planning for irradiation of thorax with ^{60}Co in fixed beam teletherapy. *Acta radiol. Ther. Phys. Biol.* 3 (1965) 342.
- STERLING T. D., PERRY H. and KATZ L. Automation of radiation treatment planning. IV. Derivation of a mathematical expression for the per cent depth dose surface of cobalt 60 beams and visualisation of multiple field dose distributions. *Brit. J. Radiol.* 37 (1964) 544.
- VOUTILAINEN A. and VAHANALO S. Experimental determination of the pulmonary tissue factor in cobalt 60 teletherapy. *Amer. J. Roentgenol.* 97 (1966) 939.

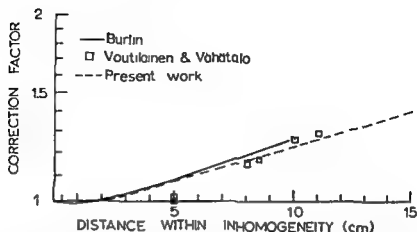


Fig. 6. Experimental results of BURLIN (1957) (SSD 50–70 cm field 10.7 cm \times 10.7 cm phantom density $\rho = 0.38$ g/cm³) VOUTILAINEN & VAHATALO (1966) (SSD 60 cm field 64–150 cm² measurements in an oesophagus) and the present study (SSD 50 cm field 10 cm \times 10 cm $\rho = 0.27$ g/cm³)

Discussion

It has been demonstrated that the per cent depth dose at the central axis of the beam can be calculated by means of three formulas, if the effect of pulmonary tissue is to be taken into account. The first formula (2) is valid in the front of the lung, the second (3) within it, and the third (4) behind it. Fig. 4 presents the values calculated in comparison with those derived by experiment for different thicknesses of the lung phantom. Fig. 5 contains a few examples of measurements with different field sizes and different positions of the cork phantom. The agreement between the experimental points and the lines calculated theoretically is seen to be rather close. Of course, the values calculated are not valid in the close vicinity of the tissue boundaries.

Interest is attached to a comparison of these results with the correction factors published earlier. A comparison is made in Fig. 6 which reveals that the SSD does not greatly affect the factors as has previously been pointed out by BURLIN (1957). The correction factor curves published by BURLIN lie slightly above the curve now presented, while the factors reported by VOUTILAINEN & VAHATALO (1966) are slightly smaller than the present ones. Details of measurements are given in Fig. 6.

BURLIN demonstrated that the correction factors reach a constant value about 6 cm behind the inhomogeneity induced by the pulmonary tissue equivalent material. Reference to Figs. 4 and 5 will show that the present results disclose no constant value. The factors increase slowly, even to a depth of about 15 cm, although the increase is so insignificant that the observation made by BURLIN is more or less valid.

Experimental arrangement The experiments were performed with a Siemens Tridoros 5 S diagnostic unit a three phase machine with 12 dry rectifiers. The tube a Bi 100/30/50 RM with 0.5 mm Al inherent filtration had a 0.6 mm and 1 mm double focus. A suitable field size and adequate limitation of the beam was obtained by means of a long cylinder the focus-film distance was 80 cm. Ferrania industrial film fine grain without intensifying screens was used.

The breast phantom was manufactured by the Minnesota Mining and Manufacturing Company and consisted of transparent non granular plastic with an effective atomic number of 6.41 and density 1.14. It had the same response to roentgen radiation as a human subject. Several objects were embedded on a horizontal plane in the middle of the phantom and included five sections of stainless steel wire placed parallel to one another and measuring 1 mm, 0.5 mm, 0.25 mm, 0.125 mm and 0.05 mm in diameter as well as gelatine capsules of air and bone dust and a section of human bone with the cancellous structure visible.

Effect of the filters upon 30 kV—35 kV roentgen radiation It is an established fact that a Fe filter due to its higher atomic weight will have a greater effect upon the softer part of the roentgen spectrum than an Al filter. The absorption in the Fe filter of photons of this energy is only of a photo-electric nature. The energy of the K radiation from iron is about 8 keV and at a distance of 80 cm this will be practically absorbed in the air. Thus the unnecessary soft radiation to the skin can be reduced in comparison with the use of only the inherent Al filter.

Results

The films were exposed to the same blackening measured by means of a Macbeth Ansco densitometer. The image qualities were examined by means of the different objects embedded in the middle of the breast phantom.

The skin exposure per film with different filters and kilovoltages was as follows:

kV	Filters	Skin exposure /Film
30	0.5 Al	24.5 R
35	0.5 Al + 0.038 Fe	8.9 R
35	0.5 Al + 0.050 Fe	4.2 R

The relative low skin exposures at 35 kV were not due to the filtration alone since the film sensitivity is somewhat greater at 35 kV than at 30 kV.

In examinations of patients with 30 kV and a 0.5 Al filter the average value of skin doses per film was about 10 R. This means that the dose to patients may

IRON FILTERS AS A MEANS OF REDUCING THE DOSE IN ROENTGEN EXAMINATION OF THE FEMALE BREAST

by

SFEN MAUDAL

Attention has long been directed to filters as being the best means of obtaining the most useful quality of roentgen radiation. THORAEUS developed multifilter combinations of tin, copper and aluminium to avoid too much soft radiation in deep therapy. These filters compared to those of pure copper, are particularly efficient around 250 kV and 300 kV. TROUT, KELL & CATHY performed a series of measurements with different aluminium filters in the range between 50 to 130 kV for the purpose of establishing a means of reducing the exposure to the patient in roentgen diagnosis. The work of BOSCHÉ & FRIK in this field must also be mentioned. These authors reported the advantages of iron over copper filters in the 60 to 150 kV roentgen radiation range.

Roentgen examination of the female breast is relatively new. The most useful quality of roentgen radiation has been found to lie in the range between 20 kV and 40 kV, the technique has been fully described by ECKEN.

The aim of the present investigation was to determine the influence of different iron filters upon the optimal image quality in relation to the radiation dose to the patient.

Experimental arrangement The experiments were performed with a Siemens Tndoros 5 8 diagnostic unit a three phase machine with 12 dry rectifiers. The tube a Bi 100/30/50 RM with 0.5 mm Al inherent filtration had a 0.6 mm and 1 mm double focus. A suitable field size and adequate limitation of the beam was obtained by means of a long cylinder the focus-film distance was 80 cm. Ferrania industrial film fine grain without intensifying screens was used.

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The relative low skin exposures at 35 kV were not due to the filtration alone since the film sensitivity is somewhat greater at 35 kV than at 30 kV.

In examinations of patients with 30 kV and a 0.5 Al filter the average value of skin doses per film was about 10 R. This means that the dose to patients may

be expected to be only half of the values obtained with the phantom. These results suggest that roentgen examination of the female breast may be performed with about 2 R per exposure.

We found after completion of our investigation that HRANITZKY & SHALEK had published a study in which aluminium filters had been added and in which the skin doses were found to vary between 2 and 23 rad per film.

Acknowledgement

The author wishes to thank K. Iversen for placing the mammography laboratory at his disposal for the present investigation.

SUMMARY

Measurement of skin exposures in roentgen examinations of the female breast demonstrated that with the use of iron filters the examinations can be performed with about 2 R per exposure.

ZUSAMMENFASSUNG

Für die Röntgenuntersuchung der weiblichen Brustdrüse wurde der Einfluss von Eisenfiltern auf die Hautbelastung erforscht und es wurde gezeigt dass ungefähr 2 R per Expositionierung genügen.

RÉSUMÉ

Des mesures de dose à la peau ont montré l'effet de filtres de fer pour l'examen radiographique du sein chez la femme. L'examen peut être fait avec environ 2 R par film.

REFERENCES

- BOSCHF H and FRIK W. Vorteile der Strahlenfilterung mit Eisen im Spannungsbereich der Röntgendiagnostik. *Fortschr Röntgenstr* 96 (1962) 136.
- FEAN R L. Mammography. Charles C Thomas Springfield 1964.
- HRANITZKY E B and SHALEK R J. Skin doses from glass and beryllium window X-ray tubes in mammography. *Radiology* 88 (1967) 668.
- THORAEUS R. A study of the ionization method for measuring the intensity and absorption of roentgen rays and of the efficiency of different filters used in therapy. *Acta radiol* (1932) Suppl No 15.
- TROUT F, DALL K, FILLEY JOHN P and CATHIEY GEORGE A. The use of filters to control radiation exposure to the patient in diagnostic roentgenology. *Amer J Roentgenol* 67 (1952) 946.
- — and LUCAS A C. Evaluation of Thoraeus filters. *Amer J Roentgenol* 85 (1961) 933.

ASPIRATION BIOPSY IN DIAGNOSIS OF PALPABLE LESIONS OF THE BREAST

Critical review of 3 479 consecutive biopsies

by

S FRANZEN and J ZAJICEK

The value of aspiration biopsy in the diagnosis of mammary carcinoma has been much discussed in the literature (STEWART 1933 MARTIN & STEWART 1936 SAYAGO 1942 ADAIR 1949 BUDD 1949 PIAGGIO BLANCO & PASEYRO 1950 SAPHIR 1952 DUSTIN JR 1953 JOHNSTON JR 1954 CORNILLON & VERHAEGHE 1955 1959 FLEMING 1955 ROSEMOND et coll 1955 TENINE 1956 GIBSON & SMITH 1957 DI PAOLA et coll 1957 TAILHEFER 1957 BETHEL 1958 GODWIN 1958 BLAUDIN DE THE 1959 SMITH et coll 1959 VIAGGIO & EGLIA 1959 MARSAN & BERTINI 1960 SHILLER VOLKOVA & AGANOVA 1960 BERG 1961 GLASSMAN 1961 KLIMANOVA 1961 DARGENT 1962 ROSEMOND 1963 VERHAEGHE 1963 ZAJDELA 1963 SODERSTROM 1966 ZAJICEK et coll 1967) Opinions on the method range from almost total rejection to enthusiastic acceptance

Aspiration biopsy is however in certain circumstances generally accepted as the diagnostic method of choice. It is commonly agreed that in inoperable carcinoma of the breast needle aspiration is preferable to surgical biopsy for confirming the

From Rad umhemmet and the Department of Clinical Cytology the Institute of Radiopathology Karolinska Sjukhuset Stockholm Sweden Submitted for publication 29 February 1968

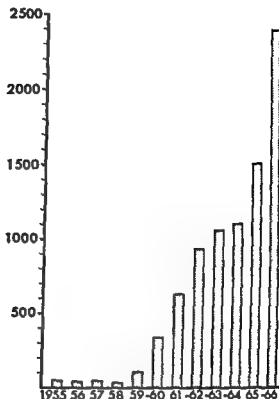


Fig. 1 Frequency of aspiration biopsy in mammary tumour diagnoses at Radiumhemmet 1955—1966

diagnosis prior to radiotherapy. For distinguishing between diffuse suppurative mastitis and carcinoma accompanied by severe inflammation, aspiration biopsy likewise is widely preferred.

The indications for aspiration biopsy in other cases may vary from clinic to clinic. In some centres its use may be confined to evacuation of cysts. The procedure is then therapeutic, but it may eliminate the need for surgery if the palpatory findings become normal after removal of the cystic contents. Other clinicians use aspiration biopsy of the breast mainly on suspicion of malignant but potentially operable lesions: a positive cytologic report is then followed by radical mastectomy without prior recourse to surgical biopsy.

At Radiumhemmet aspiration biopsy is done on all palpable lesions of the breast. Thus, it is used to establish the diagnosis before radiotherapy in presumed cancer for which surgery is judged to be contra-indicated. When surgery is intended, regardless of the result of the cytologic examination, aspiration biopsy is done to assist in planning its extent: excisional biopsy for cytologically benign or only possibly malignant lesions, and radical mastectomy when the cytologic report states carcinoma.

To investigate the usefulness of needle biopsy for revealing carcinoma of the

breast when such a wide range of indications for the procedure is used 3 479 consecutive aspiration biopsies performed at Radiumhemmet were reviewed, and the cytologic reports were compared with clinical and histologic findings. The results are now presented and the advantages and limitations of this cytologic method in the detection of mammary carcinoma in palpable lesions are discussed.

Clinical material The frequency of aspiration biopsy of the female breast at Radiumhemmet between 1955 and 1966 is recorded in Fig. 1.

The present study covers the years 1955–1963. During this period aspiration biopsy of the breast was performed on 3 479 occasions in 3 023 women who attended Radiumhemmet because of a palpable mass in mammary tissue. Of these women 86 were excluded from the present study because the aspiration biopsies were performed after surgery or radiotherapy or because surgery was delayed until six months or more after aspiration biopsy.

The conclusions concerning the diagnostic accuracy of aspiration biopsy are based on 2 937 women, 1 686 of whom were subsequently operated on. In 27 women aspiration biopsy and subsequent surgery involved both breasts; each breast is then considered as a separate case. When aspiration biopsy was done more than once before operation, only the cytologic findings from the first biopsy are reported.

Aspiration of 1 406 breasts in 1 251 women was not followed by surgery. In these cases the cytologic and clinical findings are compared. Again each breast is reported as a separate case and only the first needle biopsy is considered.

Technique of aspiration biopsy A Luer Lok syringe with a special handle which permits a single hand grip was used (FRANZEN et coll. 1960, ZAJICEK et coll. 1967). Disposable 0.6 mm needles are usually satisfactory; such a fine needle minimizes admixture of blood but a thicker needle may occasionally have to be substituted if the initial attempt indicates presence of dense fibrotic tissue, e.g. in the wall of a mammary cyst.

No anaesthesia is given. The skin is wiped with antiseptic solution and the mass is grasped with one hand in a position favourable for needling. Superficially sited lesions are held between the index finger and thumb and are punctured with a short (about 3 cm) needle. Longer needles (about 6 cm or more) are used for deeper seated lesions in voluminous breasts.

The needle having entered the tumour area the plunger of the syringe is retracted so that a vacuum is created in the system while the needle is guided in a straight line through the lesion. In order to obtain sufficient material particularly from fibrotic lesions the needle may have to be moved back and forth in

the mass up to five times and possibly inserted into different areas of the mass. Throughout this manipulation, negative pressure is maintained in the syringe by keeping the plunger retracted. When the aspiration has been completed, the pressure in the syringe is allowed to equalize before the needle is withdrawn from the tumour. It is important that no pressure difference remains in the system when the needle is withdrawn for otherwise tumour cells may be aspirated into the needle track. The syringe is disconnected from the needle, filled with air and reconnected. The contents of the needle are then carefully expressed on to a glass slide.

Preparation of the smear The aspirate is spread along the slide. Aspirate which contains blood or cystic fluid must be spread with the aid of a thick coverslip (such as used in a Burkner counting chamber) as for an ordinary blood smear. Any largish tissue fragments that collect at the end of the smear are gently squeezed by flat pressure with the coverslip used to spread the smear. If the aspirate consists of greyish, solid or semisolid material, the smear is best prepared by firm, flat pressure with the coverslip.

The fluid aspirated from cysts was discarded if it was transparent and no residual mass could be palpated. If, however, the aspirate was turbid or haemorrhagic, or if a palpable swelling persisted after the aspiration, the cystic contents were cytologically analyzed. A few drops of heparin were added to prevent clotting of haemorrhagic aspirate.

Fixing and staining of smears Methods of fixing and staining smears of biopsy aspirate have excited some controversy. In some collaborative reports from clinicians and pathologists, wet fixation and stains such as Papanicolaou or haematoxylin-eosin have been recommended in order to give maximum resemblance between the aspirated cells and their equivalents in tissue sections. One disadvantage of this method is that the aspirates dry fairly quickly, which makes for variability in fixing and staining. BERO (1961), however, accepted air drying of the smears, and use of the mentioned stains though these were originally devised for wet fixed smears or tissue section. He pointed out that the sine qua non of microscopic diagnosis is the recognition of a repeated pattern and considered the loss of microscopic detail to be compensated for by consistency in the preparation of large numbers of smears.

Haematologic experience also indicates air drying as the method of choice, but this with stains initially intended for air dried smears of blood or bone marrow. The May-Grunwald-Giemsa (MGG) stain is used as a standard by most haematologists.

Smears at Radumhemmet are usually dried in air and stained with MGG.

Whenever possible additional smears are prepared from the same specimen by immediate fixation in equal parts of ethyl alcohol and ether and stained according to Papanicolaou. This practice was introduced in order to collect material for comparison of the diagnostic merits of the two methods.

The success of the MGG stain in haematology is mainly due to its quality of disclosing cytoplasmic details such as degrees of basophilia and granulation. It stains both nuclei and cytoplasm intensively and analysis therefore requires a monolayer cell distribution. This implies that MGG staining of needle aspirate is best suited for tissues such as lymph nodes and bone marrow since the yield then is mainly individual cells which can be spread in a single layer. In malignant tumours the intercellular cohesion usually is greatly reduced (COWAN 1944), and therefore aspirate from such tumours is likewise well suited for staining with MGG. When the aspirate derives from benign tumours such as fibroadenoma and consists of large plugs of overlapping cells wet fixation and more selective staining of the nuclei e.g. with Harris haematoxylin may be preferable. Wet fixation may also be better when the aspirate is necrotic or if there is cytoplasmic degeneration for instance in material from cystic lesions.

The decision for or against supplementing air-dried smears with wet fixed smears may be made from case to case when the first slide has been spread with aspirate and macroscopically evaluated.

Cytologic and histologic examinations. All the aspiration biopsies were performed by cytologists at Radiumhemmet and in the individual cases the cytologist who read the slides had usually also performed the biopsy. Only the diagnoses made at the original reading of the slides are tabulated. When present opinion differs from the original diagnosis this is discussed in the text.

The histologic diagnoses were made in the pathology departments of the various hospitals to which the patients were referred for surgery. In the cases operated on at Karolinska Sjukhuset (about 40 per cent of the total series) the diagnoses were made at the Institute of Radiopathology. The original histologic diagnoses are used in the comparative study. Current opinion in cases with an initial histologic diagnosis of precancerous lesion is discussed separately on page 14.

Results

Series A — Aspiration biopsy findings in 1 713 breasts with subsequent histologic diagnosis

The cytologic reports on the 556 breasts (546 women) with a histologic diagnosis of benign non-neoplastic conditions are presented in Table 1.

In 19 of the 41 cases of mastitis the aspiration biopsy smears had revealed

Table 1

*Cytologic findings in 556 breasts with subsequent histological diagnosis of non neoplastic disorders —
Figures in parentheses indicate percentages*

Cytologic findings	Histologic diagnoses				Total
	Mastitis	Fat necrosis	Fibrocystic mastopathy	Fibrosing adenosis	
Fat blood or no yield	4 (9.8)	1 (16.7)	63 (12.8)	—	68
Cystic fluid	10 (24.4)	—	199 (40.4)	1 (6.2)	210
Inflammatory cells	19 (46.3)	1 (83.3)	8 (1.6)	—	37
Benign epithelium	7 (17.1)	—	171 (34.7)	9 (56.3)	187
Fibroadenoma	—	—	9 (1.8)	3 (18.8)	12
Cellular atypia	1 (2.4)	—	32 (6.5)	2 (12.5)	35
Carcinoma suspected	—	—	10 (2.0)	1 (6.2)	11
Carcinoma	—	—	1 (0.2)	—	1
Total	41	6	493	16	556

inflammatory cells, such as granulocytes, lymphocytes and histiocytes. Inflammatory cells were also present in five of the 6 cases of fat necrosis, along with degenerated fat cells and/or lipophages.

Fibrocystic disease was the histologic diagnosis in 493 breasts. The aspirate was reported to be cystic fluid in 199 of these, and benign epithelium in 171. In 9 cases of fibrocystic disease the cytologic examination suggested fibroadenoma. Cellular atypia was reported in 32 cases of the same group and carcinoma was cytologically suspected in 10 cases. A cytologic diagnosis of carcinoma was made in one case (Fig. 21), which is discussed later.

Fibrosing adenosis was found at histologic examination in 16 cases, in nine of which the cytologic report was benign epithelium and in one case cystic contents. Three cases were cytologically regarded as fibroadenomas. Cellular atypia was reported in two cases and carcinoma was suspected in the remaining case.

Table 2 concerns the 251 breasts (249 women) in which the histologic examination disclosed benign tumours. In the single case of hemangioma aspiration biopsy yielded only blood. The aspirate from 12 of the 15 lipomas consisted chiefly of fat. The cytologic report had suggested lipoma in most of these cases; this was partly based on palpation of freely mobile, fairly well defined swellings that were clinically considered to be cysts, adenomas or lipomas. Intraductal papilloma was histologically diagnosed in 11 cases, in six of which the preceding aspiration biopsy had yielded epithelium of benign appearance and in five no material or only cystic fluid.

Table 2

Cytologic findings in 251 breasts with subsequent histologic diagnosis of benign tumour — Figures in parentheses indicate percentages

Cytologic findings	Histologic diagnoses				Total
	Haemangioma	Lipoma	Intraductal papilloma	Fibroadenoma*	
Fat, blood or no yield	1	12 (80)	3 (27.3)	12 (5.4)	28
Cystic fluid	—	—	2 (18.2)	3 (1.3)	5
Inflammatory cells	—	—	—	2 (0.9)	2
Benign epithelium	—	3 (20)	6 (51.5)	66 (29.5)	75
Fibroadenoma	—	—	—	129 (57.6)	129
Cellular atypia	—	—	—	—	—
Carcinoma suspected	—	—	—	12 (5.3)	12
Total	1	15	11	224	251

* In 4 cases the histologic report also stated suspected cystosarcoma phylloides

Fibroadenoma was the histologic diagnosis in 224 cases though the reports in four of these cases suggested possible cystosarcoma phylloides. Table 2 reveals that in 129 (57.6 per cent) of this group, fibroadenoma had already been reported in the cytologic examination. In twelve cases there was cytologic suspicion of malignancy. No false positive diagnosis of carcinoma was made.

The cases of precancerous lesion and of mammary carcinoma are presented in Table 3 which also summarizes Tables 1 and 2. As already stated, the cytologic reports suggested malignancy in 23 of the 807 cases with histologically benign mastopathies. The single case in which a clear cytologic diagnosis of malignancy was followed by a histologic report of a benign condition is discussed later.

Precancerous lesions were histologically observed in 33 cases. Table 3 indicates that in four of these cases the cytologic report stated carcinoma and in four other cases suspected carcinoma. After a recent review of the histologic slides 20 of the thirty-three cases were reclassified according to modern nomenclature as intraductal carcinoma. The implications of this reclassification as regards the cytologic diagnosis are treated in the discussion.

Invasive carcinoma was present (or in six cases suspected) at histologic examination in 873 breasts (858 women). In 77 (8.8 per cent) of these histologically diagnosed carcinomas the cytologic examination did not indicate malignancy and in 17 cases (1.9 per cent) only cellular atypia was reported. Malignancy was suggested by the cytologic examination in 117 cases (13.4 per cent),

Table 3

Cytologic findings in 1 713 breasts with subsequent histologic diagnosis of benign lesion of precancerous lesion or carcinoma — Figures in parentheses indicate percentages

Cytologic findings	Histologic diagnoses			Total
	Benign lesion*	Precancerous lesion including intraductal carcinoma	Carcinoma**	
Fat blood or no yield	96 (11.9)	1 (3.0)	29 (3.3)	126
Cystic fluid	215 (26.6)	7 (21.2)	6 (0.7)	228
Inflammatory cells	34 (4.2)	—	—	34
Benign epithelium	262 (32.5)	13 (39.4)	39 (4.5)	314
Fibroadenoma	141 (17.5)	3 (9.1)	3 (0.3)	147
Cellular atypia	35 (4.3)	1 (3.0)	17 (1.9)	53
Carcinoma suspected	23 (2.9)	4 (12.1)	117 (13.4)	144
Carcinoma	1 (0.1)	4 (12.1)	662 (75.8)	667
Total	807	33	873	1 713

* In 4 cases the histologic report stated suspected cystosarcoma phyllodes

** In 6 cases the histologic report was suspected invasive carcinoma

but the evidence was considered to be insufficient to warrant a definite recommendation of radical surgery. In the remaining 662 cases (75.8 per cent) the cytologic report stated malignancy and advised radical operation.

Series B — Aspiration findings in 1 406 breasts without histologic diagnosis

The cytologic reports and the clinical findings in the breasts in which aspiration biopsy was not followed by surgery are presented in Table 4. It is seen that 37 cases were clinically classified as simple mastitis, and that cytologic confirmation of this diagnosis was obtained in 26 cases. In 340 of the 583 breasts with fibrocystic disease, aspiration biopsy yielded benign epithelial cells. Large solitary cysts were clinically considered to be present in 139 cases, in 96 of which aspiration biopsy yielded cystic fluid.

The clinical diagnosis in 214 cases was simply tumour without further specification. The cytologic examination in 98 of these cases indicated that the tumour was a large cyst. In the 120 cases clinically described as benign adenoma, the most common cytologic diagnoses were cyst (40 cases) and fibroadenoma (29 cases).

Table 4

Cytologic and clinical findings in 1 406 breasts without histologic diagnosis

Cytologic findings	Clinical findings							Total
	Mastitis	Fibro-cystic disease	Cyst	Tumour	Adenoma	Carcinoma suspected	Carcinoma	
Fat blood or no yield	3	118	5	74	13	23	3	239
Cystic fluid	5	77	96	98	40	19	80	355
Inflammatory cells	26	22	1	25	4	4	3	85
Benign epithelium	2	340	20	—	32	39	1	434
Fibroadenoma	1	16	15	16	29	—	—	77
Cellular atypia	—	10	2	1	2	1	—	16
Carcinoma (suspected)	—	—	—	—	—	—	24	24
Carcinoma	—	—	—	—	—	1	175	176
Total	37	583	139	214	120	87	226	1 406

Carcinoma was clinically considered likely in 87 cases. In 43 of them carcinoma had previously been found in the other breast. The cytologic report stated carcinoma in only one of these 87 cases.

Carcinoma was clinically considered to be present in 226 cases and was cytologically confirmed in 175 cases (77.4 per cent). In a further 24 cases (10.6 per cent) malignancy was cytologically suspected. Thus in 27 cases (11.9 per cent) the aspiration biopsy smears were negative for carcinoma and in twenty of these cases the aspirate consisted predominantly of cystic fluid. Poor general health or refusal of permission to operate were the reasons why surgical biopsy and thereby histologic examination were not done in this group of cases.

Discussion

At Radiumhemmet aspiration biopsy of palpable lesions of the breast and other organs is performed by cytologists and as a rule the cytologist who analyzes the smears prepared from the aspirate has also done the biopsy. He therefore has the advantage of direct confrontation with the clinical problem and can form his own opinion of the case. He can also collect additional information

while needling the lesion and preparing the smear, during the needling he will learn more about the size, site and consistency of the mass. The consistency — soft, solid or fibrotic — may have implications regarding the cellularity of the aspirate. The presence of capsular tissue may occasionally be apprehended, for example in some cases of lipoma, fibroadenoma or cyst.

Naked eye inspection of the aspirate may also be helpful. Indeed, it is essential to assess the adequacy of the sample, and consequently whether or not the biopsy should be repeated. The aspirate from mammary lesions may be fluid, semisolid or solid, possibly with admixture of blood. Fluid aspirate suggests that a cyst is present and this should prompt the examiner to reappraise the lesion after the aspiration. If any residual mass can then be palpated, a second aspiration should be done. Inspection of solid aspirate may likewise be rewarding. When spreading solid aspirate, the experienced examiner can make a fairly accurate macroscopic judgement of whether it contains plugs of tumour tissue or consists predominantly of necrotic or amorphous material. Findings of the latter types should lead to repetition of the biopsy, possibly from the periphery of the mass from where well preserved cell populations may be more easily aspirated.

At this stage the examining cytologist may also decide if he will prepare both air dried smears and wet fixed smears, the latter to be stained according to Papanicolaou or with other, more specific stains used in modern cytochemistry. If a circumscribed mass yields transparent material, which when spread on a glass slide resembles fat, lipoma can be considered as the diagnosis. But should the examiner be uncertain if such aspirate has been sampled from within the mass, the biopsy should be repeated since the cytologic report of lipoma will stand or fall on that judgement.

Consequently, the cytologic diagnosis of mammary lesions is based on a summation of the clinical assessment prior to aspiration biopsy, the observations made during needling of the mass, and the microscopic evaluation of the slides. The foregoing remarks further indicate that optimal conditions for diagnostic work with aspiration biopsy are obtained when the same cytologist observes the clinical features of the case during the biopsy and can personally handle the fragile aspirated material when spreading it on the slides. At present such optimal conditions exist in certain centres, such as Radiumhemmet in Stockholm, Fondation Curie in Paris (ZAJDELA 1967) and Centre Oscar Lambret in Lille (CORNILLOT 1967), France. When slides of aspirate are delivered to the cytologist from other departments or hospitals, much depends upon the amount and relevance of the written information and even more on the skill with which this material has been obtained and the slides have been prepared. If the clinical information is inadequate and the slides are not representative or are badly prepared, the diagnostic results will be poor (SODERSTROM 1966, p. 153).

The main purpose of the present paper has been to evaluate the usefulness of fine needle biopsy in the diagnosis of mammary carcinoma. In the following we shall also briefly deal with other common disorders of the breast such as simple mastitis, cystic mastopathy, fibrosing adenosis and fibroadenoma. The discussion will be confined to cases in which aspiration biopsy was followed by surgery and histologic diagnoses therefore were available for comparison, i.e. the cases listed in Tables 1, 2 and 3.

Mastitis. The aspirate in diffuse suppurative mastitis most commonly consists of fluid, semisolid or solid material containing numerous inflammatory cells such as granulocytes, lymphocytes, monocytes, foam cells and phagocytes. The diagnosis can then be readily made. Sometimes, however, large sheets of foam cells and of histiocytes with enlarged nuclei present problems for the inexperienced examiner (Fig. 2, b and c). But careful analysis of the general appearance of the smear should clearly reveal the benign nature of such aggregates. The transitional forms of foam cells and of sheets of histiocytes in these smears can be traced from clusters of apparently normal mammary epithelium. PAPANICOLAOU & MADDI (1959) demonstrated the epithelial origin of the foam cells and the histiocytes by experimental transformations in tissue cultures on clusters of mammary epithelial cells. They found gradual transformation of epithelial cells into free foam cells that could phagocytize erythrocytes which were purposely introduced into the cultures. The ductal origin of vacuolated phagocytes in secretions from the mammary gland now seems to be generally accepted (Koss 1961).

Fibrocystic disease. Of the 556 benign mastopathies listed in Table 1, 88.7 per cent were histologically classified as fibrocystic. The most common yield at aspiration biopsy in these cases (in 40.4 per cent of the group) was a fluid which could be clear, yellow, brown, greenish or blood stained.

The presence of single or multiple cysts hampers diagnostic palpation of the breast. When cystic fluid is removed by aspiration the lesion can be more easily evaluated. If no residual underlying mass is palpable the affected site may or may not be excised, depending upon the routine practice at the clinic in question.

Cytologic study of clear fluid aspirated from these cysts generally reveals only foamy phagocytes. When a mass can be palpated after the aspiration, however, the fluid is usually more cell rich with inflammatory cells as well as foamy phagocytes. Some smears contain epithelial cells with varying degrees of atypia and in papillary formation. A palpable mass persisting after aspiration of a presumed cyst is almost always excised. In such cases, therefore, the cytologist's

report will have little influence on the further management, except in the rare instances in which malignant cells from a carcinoma growing in the cystic wall are detected in smears of the fluid aspirate.

Benign epithelial cells without noteworthy admixture of cystic fluid were aspirated in 34.7 per cent of the cases with fibrocystic mastopathy. Smears from such lesions as a rule reveal only a few tightly packed plugs of cells. Dissociated cells are rarely seen, and if present usually display signs of degeneration (Fig. 3a). Naked nuclei with bipolar form are often encountered, however (Fig. 3b).

In most cases, there is no obvious cellular atypia, and the cytologic recognition of a benign condition presents no problem. But if, instead of this homogeneous appearance, plugs of apparently benign cells are intermingled with clusters of atypical cells, and particularly if the smears possess intact free ductal cells with nuclear atypia, the possibility of the presence of a precancerous lesion or early carcinoma must be considered (Fig. 3c). Depending upon the gravity of the cytologic indication of malignancy, the cytologist may advise frozen sectioning in connection with excision of the lesion.

In ten cases of fibrocystic mastopathy the cytologic report suggested carcinoma (Table I), in all of which the mass and its surrounding tissue were extirpated. The cytologic and histologic slides from these cases have been reviewed. The histologic diagnosis was upheld, but in the light of present cytologic experience the slides prepared from the biopsy aspirate would be considered to indicate malignancy in only six of the cases. In one of these six cases (Fig. 6a), a carcinoma was found just beneath the operation scar two years after aspiration biopsy and excision of the initial mass, and cancerous lymph nodes were present in the axilla. The other five cases in which cytologic smears were still considered to suggest malignancy are alive and apparently free from cancer after four to seven years of observation.

The cytologic report stated carcinoma in one case (Fig. 2a) and mastectomy was performed later at another hospital. The examining pathologist reported fibrocystic mastopathy. The cytologic slides were then re-examined and, as the diagnosis of malignancy was confirmed, a study of additional tissue specimens was recommended. Unfortunately, however, the excised breast was no longer available for further analysis. This patient is apparently free from cancer five years after mastectomy.

Fibrosing adenosis. Contrary to the opinion that fibrosing adenosis is histologically 'the commonest lesion confused with breast cancer' (STEWART 1950), this lesion has not caused major problems in the present series, the reason probably being that the lesions were usually very small and fibrotic. Needling as a rule

yielded only a few atypical cells most often in acinar arrangement and intermingled with naked nuclei of benign appearance, quite unlike the findings in a carcinoma smear. Malignancy was considered possible in only one case in which cell rich smears were obtained. Review of the slides revealed plugs of cells partly in acinar arrangement and with marked anisonucleosis (Fig 4), which had aroused suspicion of early carcinoma.

If the cytologic requirement for a diagnosis of mammary carcinoma is that the smear must be dominated by unmistakable cancer cells this should preclude false positive reports of malignancy in fibrosing adenosis.

Fibroadenoma. This was the most common of the benign mammary tumours in the series (Table 2) representing 89.2 per cent of the total 251 benign tumours. Clinical examination characteristically reveals a firm, freely mobile mass which may be confused with cyst or lipoma, however, and in elderly patients also with carcinoma. The expected aspirates in these lesions are fluid, fat and carcinoma cells respectively but in fibroadenoma benign mammary epithelium. This last finding, in combination with palpation of a well circumscribed mass indicates fibroadenoma.

In most cases of fibroadenoma smears prepared from biopsy aspirate contain numerous clusters of epithelial cells and also free dissociated cell elements with predominance of naked bipolar nuclei (Fig 5). This contrasts with paucity of cellular material in aspirate from cases of fibrocystic disease of the breast.

Whether or not and in what frequency the cytologic features described can provide a sufficient basis for diagnosis of fibroadenoma in the absence of a clinical report of a well circumscribed tumour is not yet known. This question will be tackled in future studies. At present it can only be placed on record that of the 224 cases of histologically demonstrated fibroadenoma 57.6 per cent had already been thus diagnosed by the aspiration biopsy method.

A false positive diagnosis of fibroadenoma was made from slides of aspirate in only 12 of the 583 cases with a subsequent histologic diagnosis of benign mammary lesions other than fibroadenoma (5.6 in Table 1 and 27 in Table 2). Of these twelve cases nine had fibrocystic mastopathy and three had fibrosing adenosis.

Carcinoma was cytologically suspected in 12 of the cases histologically classified as fibroadenoma. The histologic diagnosis in one of these cases was suspected cystosarcoma phyllodes. When the cytologic slides of the remaining eleven cases were reviewed it was decided that with present experience only four cases would be labelled as possibly malignant and in all these four cases the tumour and surrounding tissues were excised. One of the patients (with histologic diagnosis of fibroadenoma) was found 13 months later to have a subcutaneous carcinoma.

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yielded only a few atypical cells most often in acinar arrangement and intermingled with naked nuclei of benign appearance quite unlike the findings in a carcinoma smear. Malignancy was considered possible in only one case in which cell rich smears were obtained. Review of the slides revealed plugs of cells partly in acinar arrangement and with marked anisonucleosis (Fig 4) which had aroused suspicion of early carcinoma.

If the cytologic requirement for a diagnosis of mammary carcinoma is that the smear must be dominated by unmistakable cancer cells this should preclude false positive reports of malignancy in fibrosing adenosis.

Fibroadenoma This was the most common of the benign mammary tumours in the series (Table 2) representing 89.2 per cent of the total 251 benign tumours. Clinical examination characteristically reveals a firm freely mobile mass which may be confused with cyst or lipoma however and in elderly patients also with carcinoma. The expected aspirates in these lesions are fluid fat and carcinoma cells respectively, but in fibroadenoma benign mammary epithelium. This last finding in combination with palpation of a well circumscribed mass indicates fibroadenoma.

In most cases of fibroadenoma smears prepared from biopsy aspirate contain numerous clusters of epithelial cells and also free dissociated cell elements with predominance of naked bipolar nuclei (Fig 5). This contrasts with paucity of cellular material in aspirate from cases of fibrocystic disease of the breast.

Whether or not and in what frequency the cytologic features described can provide a sufficient basis for diagnosis of fibroadenoma in the absence of a clinical report of a well circumscribed tumour is not yet known. This question will be tackled in future studies. At present it can only be placed on record that of the 224 cases of histologically demonstrated fibroadenoma 57.6 per cent had already been thus diagnosed by the aspiration biopsy method.

A false positive diagnosis of fibroadenoma was made from slides of aspirate in only 12 of the 583 cases with a subsequent histologic diagnosis of benign mammary lesions other than fibroadenoma (55.6 in Table 1 and 27 in Table 2). Of these twelve cases nine had fibrocystic mastopathy and three had fibrosing adenosis.

Carcinoma was cytologically suspected in 12 of the cases histologically classified as fibroadenoma. The histologic diagnosis in one of these cases was suspected cystosarcoma phyllodes. When the cytologic slides of the remaining eleven cases were reviewed it was decided that with present experience only four cases would be labelled as possibly malignant and in all these four cases the tumour and surrounding tissues were excised. One of the patients (with histologic diagnosis of fibroadenoma) was found 13 months later to have a subcutaneous carcinoma.

report will have little influence on the further management, except in the rare instances in which malignant cells from a carcinoma growing in the cystic wall are detected in smears of the fluid aspirate.

Benign epithelial cells without noteworthy admixture of cystic fluid were aspirated in 34.7 per cent of the cases with fibrocystic mastopathy. Smears from such lesions as a rule reveal only a few tightly packed plugs of cells. Dissociated cells are rarely seen, and if present usually display signs of degeneration (Fig. 3a). Naked nuclei with bipolar form are often encountered, however (Fig. 3b).

In most cases, there is no obvious cellular atypia, and the cytologic recognition of a benign condition presents no problem. But if, instead of this homogeneous appearance, plugs of apparently benign cells are intermingled with clusters of atypical cells, and particularly if the smears possess intact free ductal cells with nuclear atypia, the possibility of the presence of a precancerous lesion or early carcinoma must be considered (Fig. 3c). Depending upon the gravity of the cytologic indication of malignancy, the cytologist may advise frozen sectioning in connection with excision of the lesion.

In ten cases of fibrocystic mastopathy the cytologic report suggested carcinoma (Table 1), in all of which the mass and its surrounding tissue were extirpated. The cytologic and histologic slides from these cases have been reviewed. The histologic diagnosis was upheld, but in the light of present cytologic experience the slides prepared from the biopsy aspirate would be considered to indicate malignancy in only six of the cases. In one of these six cases (Fig. 6a), a carcinoma was found just beneath the operation scar two years after aspiration biopsy and excision of the initial mass, and cancerous lymph nodes were present in the axilla. The other five cases in which cytologic smears were still considered to suggest malignancy are alive and apparently free from cancer after four to seven years of observation.

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Table 5

*Histologic reclassification of 33 cases with original histologic diagnosis
preinvasive mammary lesion*

Cytologic findings	Histologic grading		
	I	II	III
Benign or no cellular material	13	9	2
Cellular atypia	—	1	—
Carcinoma suspected	—	2	2
Carcinoma	—	1	3
Total	13	13	7

This analysis of the data in Table 5 indicates that when needle biopsy smears are considered to indicate carcinoma and the case is histologically classified as intraductal carcinoma it belongs to the group of intraductal carcinomas for which histologic and clinical experiences advocate management as for invasive carcinoma.

Mammary carcinoma. The histologically diagnosed cases of mammary carcinoma are included in Table 3. The cytologic reports from aspiration biopsy in these cases can be grouped as negative, suggestive of carcinoma or positive for carcinoma.

Malignancy was histologically proven in 867 cases and was considered probable in 6 cases. A negative cytologic report as regards malignancy was given in 94 cases; the yield being described as acellular material in 35 cases, benign cells in 42 cases, and atypical cells in 17 cases.

Failure to demonstrate the presence of carcinoma in a cytologic study of needle biopsy aspirate was thus due either to failure to obtain cells from the target or to recognize the malignant nature of the aspirated cells. The cytologic slides from the 94 cases of carcinoma with negative cytologic reports were therefore re-examined in order to analyze the respective importance of these factors in the series. Indubitable carcinoma cells were then detected in 21 cases and possibly malignant cells were seen in 10 cases (as exemplified in Fig. 8). The false negative cytologic diagnoses in 31 (32.9 per cent) of the 94 cases could therefore be attributed to lack of experience in reading the slides.

Review of the slides in the remaining 63 cases confirmed the absence of recognizably or suspectedly malignant cells in the smears of biopsy aspirate. In two cases no mass was palpable in the breast (these cases should properly have

with axillary lymph node metastases (Fig 6b). The other three patients are apparently free from carcinoma 5 to 6 years postoperatively.

'Precancerous lesion', intraductal carcinoma 'Precancerous' was used in the histologic reports of 33 cases to describe lesions that were considered by the examining pathologists not to fit any generally accepted label but to be in some way related to malignancy (For a review of the literature on such lesions, the reader is referred to STEIN 1967). In these cases, the slides were collected and reviewed for a correlation of the cytologic and histologic observations. The tumours were classified as groups I, II, or III according to the histologic observations.

Cases with atypical intraductal proliferation of a type that prompts pathologists to recommend careful follow up, and immediate removal of all palpable lesions for histologic study, were placed in group I. Thirteen cases belonged to this group. Group II comprised cases with marked intraductal proliferation, and a general pattern closely resembling intraductal carcinoma but with insufficient cellular atypia to suggest the presence of undetectable invasive growth. Depending upon the extent of the lesion and the general clinical picture, simple mastectomy is usually recommended in such cases; there were thirteen in our series. Cases with the histologic appearances of intraductal carcinoma, and in which the cell atypia suggested undetectable invasive growth, were placed in group III. With this picture, radical mastectomy is generally advised. Seven cases belonged to group III.

The cytologic reports in the histologically reclassified cases of 'precancerous lesion' are collected in Table 5. None of the thirteen cases in group I were cytologically malignant. Of the thirteen cases in group II, two were thought to be carcinoma and one was cytologically malignant. The cytologic examination was followed in this case by simple mastectomy; the patient is well after about 4 years of observation. The histologic examination and the cytologic features of this case are given in Fig 7 a and b. Comparison between the cells in the smear and those in the tissue section indicates that the histologic specimen cannot be considered representative of the tumour. The aspirated cells display characteristics of invasive carcinoma (cf Fig 9, c and f).

Of the seven cases in the histologic group III, two were cytologically considered malignant and three were stated to be carcinoma. Of these last three cases, two underwent simple mastectomy and one radical mastectomy. One of the two simple mastectomies after two years displayed appearances of metastatic axillary carcinoma, and death occurred from systemic dissemination one year later (Fig 7, c and d). The two other patients are apparently well after 4 and 5 years, respectively.

Table 5

Histologic reclassification of 33 cases with original histologic diagnosis precancerous mammary lesion

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The main reason why diagnostic accuracy is higher in clinically manifest carcinoma is the abundance of malignant cells in the aspirated specimen. In early carcinoma fine needle aspirate as a rule contains only a few malignant cells and correspondingly greater caution must be observed when the report is formulated. The cytologist who recommends radical surgery in such a case must bear in mind that it is upon the histologic examination of the excised tissue that the necessity for the operation will be retrospectively judged. In the present state of cytologic knowledge a definite statement of mammary carcinoma should not be based upon the presence of a few carcinoma like cells scattered among normal or atypical epithelial elements. Predominance of unmistakable cancer cells should be required (Figs 9 to 12).

Among our 807 cases histologically diagnosed as benign mammary lesions there was only one definite cytologic report of malignancy (p. 12). Since re-examination of the slides prepared from the biopsy aspirate in this case disclosed that the cell population consisted almost exclusively of indubitable cancer cells it is probable that the negative histologic report was due to incomplete exploration of the breast. The palpable mass in this case was less than 1 cm in diameter. Such small tumours are usually studied by local excision when frozen or paraffin embedded sections should readily reveal if carcinoma is present. If the carcinoma is clinically advanced study of the whole breast likewise generally gives ready histologic confirmation of a cytologic diagnosis of malignancy. But when as in the case under discussion a scarcely palpable lesion is revealed by aspiration biopsy to be carcinoma and the whole breast is fixed in formalin and sent for histologic examination even close collaboration between cytologist, surgeon and pathologist may not avail to secure proof of malignancy. In some such cases we have succeeded in establishing the diagnosis only after study of serial sections from 10 to 20 specimens of mammary tissue. Because this difficulty is recognized we sometimes recommend a frozen section after local excision and before radical surgery even if we are convinced from the cytologic examination that a carcinoma is present viz. in clinically doubtful cases when the histologic examination will not be made at the Institute of Radiopathology.

It is thus clear that when fine needle biopsy is adopted for routine use in the diagnosis of mammary carcinoma heavy demands are made on the cytologist's formulation of his report and on the clinician in evaluating it. The danger of false positive and false negative cytologic diagnoses in this condition has frequently been demonstrated in the literature. Some pertinent data are presented in Table 6. Only series with 80 or more verified carcinoma cases are included in this table.

The total of cases surveyed in Table 6 is 324, all of which were studied both histologically and cytologically. The histologic studies revealed carcinoma in

been excluded from this series of palpable mammary lesions), the puncture was made blind, since previous aspiration biopsies of enlarged axillary lymph nodes had indicated carcinoma, most probably metastatic from a primary mammary tumour.

Of the 61 cases with a palpable mass and false negative cytologic reports, 47 per cent displayed some clinical signs of mammary carcinoma, such as dimpling of the skin, retraction of the nipple or fixation to muscle. The corresponding figure in the 117 cases in which sufficient cellular material was obtained to permit a cytologic indication of mammary carcinoma (Table 3) was only 44 per cent. In our opinion, therefore, the main reason for the false negative reports in these cases was not failure to reach the target, but the inability to collect malignant cells from tumours that were possibly fibrotic or had a relatively low cell content. This assumption is supported by the fact that repeat needle biopsy in nine of the false negative cases yielded carcinoma cells in only three cases. A more detailed analysis of this problem will be attempted in later investigations, when the cellularity of smears prepared from biopsy aspirate in mammary carcinoma will be compared with the histologic features in the same cases.

'Suspected carcinoma' was stated in the cytologic report in 117 of the histologically positive cases (Table 3). This cytologic diagnosis implies that the examining cytologist was fairly sure that carcinoma cells were present but was unwilling to accept responsibility for a radical operation before his opinion had been confirmed by excisional biopsy and frozen sectioning (Fig. 3c). The justification of this attitude is apparent from Tables 1 and 2, 23 cases (11 in Table 1 and 12 in Table 2) were thus cytologically considered possibly malignant but subsequent histologic analysis revealed benign lesions in 22 cases and probable cystosarcoma phyllodes in one case. As already stated, present experience would, in addition to the last case, uphold the cytologic probability of malignancy in only ten of these twenty-three cases. However, since in two of the ten cases a carcinoma formed beneath the scar after local excision of the lesion, careful follow-up would seem advisable when an experienced cytologist has suspected malignancy, even though a negative histologic report has been given.

Carcinoma was cytologically diagnosed in 662 (75.8 per cent) of the histologically confirmed cases in Table 3, in these cases the cytologist recommended radical operation. Some of the mentioned clinical signs of carcinoma were present in 64 per cent of the 662 cases at the time of aspiration biopsy. If it is recalled that the frequency of such clinical signs was 44 per cent in the cases cytologically thought to be malignant and 47 per cent in the cytologically false negative cases, it is evident that the stage of the disease had some bearing on the formulation of the cytologic report.

Finally, in comparing published series of cases one must also take into account that skill in performing the needle biopsies and in reading the slides may not have been equal when the respective series were begun. This too may help to explain variations in the results.

The improvement that can be expected as experience accumulates can be seen by comparing our total series (from 1955 to 1963) with the results obtained in the year 1962 (ZAJICEK 1965), i.e. after many years of routine performance of aspiration biopsy and long practice in reading of the slides. In that year 417 women underwent aspiration biopsy of the breast and subsequent mammary surgery. In 190 of these the histologic examination revealed carcinoma (59.4 per cent of the 190 were clinically considered to be carcinoma prior to the aspiration biopsy examination). The cytologic report stated carcinoma in 151 of the 190 histologically proven carcinoma cases and suspected malignancy in 24 others of the same group. Thus in 15 cases (7.9 per cent) a cytologically negative report was given. This percentage of false negatives compares well with the 7.4 per cent in the ZAJDELA (1953) study and is the lowest figure that we have as yet obtained. Such a degree of accuracy is probably obtainable only when the cytologist who reads the slides also performs the aspiration biopsy and has had long experience in these fields. Repeat biopsies after negative reports in clinically doubtful cases may to some extent further improve the results. But since even repeated negative needle biopsies do not ensure that a lesion is benign surgical biopsy should be performed in all clinically doubtful but cytologically negative cases.

No false positive cytologic diagnosis of mammary carcinoma was made during 1962. We believe that the possibility of false positive diagnoses for this tumour may be disregarded if the cytologist is fully conversant with the morphology of the cells of the mammary gland in various pathologic conditions and if he respects the mentioned reservations concerning cases of early carcinoma.

The possibility of risk to the patient is another important question. In the present series of more than 3 000 cases there were no significant complications of needle biopsy of the breast. Haematomas occasionally formed, particularly in carcinomatous breasts, but these haematomas did not cause appreciable discomfort. Much more important is the possible danger of malignant dissemination. No matter how fine are the needles used for aspiration biopsy the procedure will inevitably produce microtrauma in its passage through the tissues (Fig. 13) with consequent risk of tumour spread locally via the needle track or distally through punctured blood or lymph vessels. In our series, however, we found no clinical signs of local seeding of carcinoma following aspiration biopsy, nor is this seeding to be expected, since when a carcinoma is proven it is either widely excised or is irradiated.

Table 6

Frequencies of false positive and false negative reports from aspiration biopsy in cases of histologically verified mammary gland lesion

Literature	No of breasts	Histologically proven carcinoma		Aspiration biopsy			
				False positives		False negatives	
		No	%	No	%	No	%
CORNILLOT & VERHAEGHE (1959)	500	258	(51.6)	4	(1.7)	41	(15.9)
SMITH et coll (1959)	202	80	(39.6)	3	(2.5)	19	(23.8)
SHILLER VOLKOVA & AGAMOVA (1960)	263	165	(62.7)	4	(4.1)	44	(26.7)
ZAJDLA (1963)	600	417	(69.5)	1	(0.5)	31	(7.4)
Present series	1 680*	873	(52.0)	1	(0.1)	94	(10.8)
Total	3 245	1 793	(55.3)	13	(0.9)	229	(12.8)

* 33 cases histologically considered as precancerous lesion not included

1 793 cases. Among the remaining histologically benign cases there were 13 (0.9 per cent) cytologically stated to be carcinoma, of these thirteen false positive cases no less than seven were histologically proved to be fibroadenoma.

Failure of the aspiration biopsy cytologic method to disclose malignancy occurred in 229 of the carcinoma cases in Table 6. The frequency of false negative reports varied however widely, from 7.4 per cent (ZAJDLA 1963) to 26.7 per cent (SHILLER VOLKOVA & AGAMOVA 1960). These differences become more understandable if the probable variations in the composition of the separate series are considered. Thus, the percentages of histologically proven carcinoma cases ranged from 39.6 (SMITH et coll 1959) to 69.5 (ZAJDLA 1963). The selection of cases for aspiration biopsy and subsequent surgery may influence the accuracy of the cytologic diagnosis.

Another potential influence on the cytologic report is the number of aspiration biopsies made in the particular case. In the present series and in that reported by SMITH et coll (1959), only the first biopsy readings are tabulated. Repetition of biopsies after initial negative reports may be expected to reduce the number of false negative diagnoses, the reduction was from 23.8 to 7 per cent in the series presented by SMITH et coll (1959).

Whether the cytologist himself performs the aspiration biopsy, as in the present series and in that of ZAJDLA (1963) and of CORNILLIOT & VERHAEGHE (1959) or reads slides sent in from outside sources is yet another factor of possible importance.

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REFERENCES

- ADAIR F E Surgical problems involved in breast cancer *Ann roy Coll Surg Engl* 4 (1949) 360
- BERG J W The aspiration biopsy smear *In* *Diagnostic cytology and its histopathologic bases* p 311 Edited by L G Koss J B Lippincott Co Philadelphia 1961
- and ROBBINS G F A late look at the safety of aspiration biopsy *Cancer* 15 (1967) 876
- BETHIEL E P A La mammocytologie Étude critique de ses possibilités diagnostiques D P Tsib Paris 1958
- BLAUDIN DE THE G La valeur de la ponction à l'aiguille fine dans le diagnostic carcinologique M Leconte Marseille 1959
- BUDO J W Evaluation of needle aspiration technic in breast lesions *Radiology* 52 (1949) 507
- COMAN II R Decreased mutual adhesiveness a property of cells from squamous cell carcinomas *Cancer Res* 4 (1944) 675
- CORNILLOT M (1967) Personal communication
- et VERHARCHE M Confrontation clinique et cytologique dans les tumeurs du sein *Cancérologie* 2 (1955) 204
- — Données cytologiques dans les ponctions de tumeurs du sein *Path et Biol* 7 (1959) 793
- DARGENT M M Diagnostic des tumeurs du sein *J Méd Lyon* 43 (1962) 97
- DUSTIN JR P Note sur le rôle de la ponction biopsie dans le diagnostic du cancer *Acta chir belg* 52 (1953) 535
- FLEMING R M Cytologic studies in lesions of the breast Findings in nipple secretions and aspirates from tumors *Sth med J* 48 (1955) 74
- FRANZEN II GIERTZ G and ZAPCEK J Cytological diagnosis of prostatic tumours by trans rectal aspiration biopsy A preliminary report *Brit J Urol* 32 (1960) 193
- GIBSON A and SMITH G Aspiration biopsy of breast tumours *Brit J Surg* 45 (1957) 236
- GLASMAN J A Aspiration biopsy for detection of carcinoma of the breast A critique *J int Coll Surg* 36 (1961) 195
- GODWIN J T Validity of aspiration biopsy in cytologic diagnosis *Acta Un int Cancer* 14 (1958) 466
- JOHNSTON JR J H Aspiration as diagnostic and therapeutic procedure in cystic disease of the breast *Ann Surg* 139 (1954) 635
- KLINANOVA Z F Cytological examination of breast tumour punctates *Vop Onkol* 7 (1961) 11
- KOSS L G *Diagnostic cytology and its histopathologic bases* J B Lippincott Co Philadelphia 1961
- MARSAN C et BERTINI II La place des méthodes cyto ologiques dans le diagnostic des tumeurs du sein *Path et Biol* 8 (1960) 343
- MARTIN H II and STEWART F W The advantages and limitations of aspiration biopsy *Amer J Roentgenol* 35 (1936) 245
- DI PAOLA G RENEY SOLA E T y LOPEZ BIEL R La punción de los nodulos mamaros *Pren méd argent* 44 (1957) 549
- PAPANICOLAOU G N and MADDI F A Further observations on the behavior of human endometrial cells in tissue culture *Amer J Obstet Gynec* 78 (1959) 156
- PIAGGIO BLANCO R A y PASEYRO P El citograma obtenido por punción y sus aplicaciones al

Distal dissemination via blood or lymph vessels, with its unfavourable implications for prognosis, is a more problematic aspect. It has been carefully investigated by a research group at the Memorial Center in New York (ROBBINS et coll. 1954, BFRÉ & ROBBINS 1962). They registered the survival times in 1406 cases of mammary carcinoma that were submitted to radical surgery and compared the survival rates of those with and, respectively, without aspiration biopsy. The two groups did not differ as regards ten year survival rates. The writers therefore concluded that aspiration biopsy is not detrimental to the patient and that 'clinically, no reason can be found not to use aspiration biopsy when it is indicated'.

Acknowledgement

The authors take this opportunity of thanking Prof. Lars Santesson of the Institute of Radiopathology for his review of the histologic characteristics of the tumours.

SUMMARY

The value of aspiration biopsy in carcinoma of the breast was studied in 3119 breasts in 2937 women over a nine year period. In 1406 of these breasts no histologic confirmation of the diagnosis was made but in 1713 breasts the cytologic findings could be compared with the histologic reports after surgery. The accuracy of cytologic examinations of biopsy aspirate is evaluated from the present series and from reports in the literature.

ZUSAMMENFASSUNG

Der Wert der Punktionseytologie bei der Diagnose des Brustkrebses wurde über eine Reihe von Jahren an 2937 Frauen mit Veränderungen in 3119 Brustdrüsen studiert. In 1406 von diesen Fällen wurde keine histologische Diagnose gestellt. Eine solche war bei 1713 Brustveränderungen vorhanden, sodass man hier die zytologischen Befunde mit den histologischen vergleichen konnte. Die Zuverlässigkeit der Punktionsmethode wurde auf Basis der eigenen Resultate und derjenigen in der Literatur kritisch geprüft.

RÉSUMÉ

Les auteurs ont étudié l'intérêt de la biopsie par aspiration dans le cancer du sein sur 3119 seins chez 2937 femmes sur une période de 9 ans. Dans 1406 de ces seins il n'y a pas eu de confirmation histologique du diagnostic mais dans 1713 seins le résultat de l'examen cytologique a pu être comparé avec le résultat histologique après opération. Les auteurs jugent l'exactitude de l'examen cytologique dans la biopsie par aspiration d'après la présente série et d'après la littérature.

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MODULATION TRANSFER FUNCTION OF THE INTENSITY DISTRIBUTION OF THE ROENTGEN FOCAL SPOT

by

EIICHI TAKEYAKA KOJIRO KINOSHITA and ROKUHiko NAKAJIMA

In roentgen image transmission systems many factors are basically related to image quality. Some of the intensity distributions of the *roentgen focal spot* and its modulation transfer function (MTF) have been experimentally measured. However no definite standardization of the intensity distribution of the focal spot and no generalized study of relationships to the modulation transfer function seem to have been made (see NBS Handbook No. 89 (1963)).

The intensity distribution of the focal spot in this report expanded to symmetry and anti symmetry components on a base of rectangular function. The parameters of the symmetry and anti symmetry components are presumed and the relations to the modulation transfer function are clarified. Thus the effective intensity distributions of the focal spot are standardized by the use of its modulation transfer function. These results are indispensable for the analysis and standardization of roentgen systems such as roentgen television and cineradiographic equipment and are of basic importance for the study and interpretation of roentgen images.

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- diagnóstico de las afecciones de la glandula mamaria *An Fac Med Montevideo* 35 (1950) 1001
- ROBBINS G I, BROTHERS III J H, FERRIART W F and QUAN S Is aspiration biopsy of breast cancer dangerous to the patient? *Cancer* 7 (1954), 774
- ROSEMOND G P Differentiation between the cystic and solid breast mass by needle aspiration *Surg, Clin N Amer* 43 (1963) 1433
- BURNETT W E, CASWELL H T and McALEER D J Aspiration of breast cysts as a diagnostic and therapeutic measure *Arch Surg* 71 (1955) 223
- SAPIR O Early diagnosis of breast lesions *J Amer med Ass* 150 (1952), 859
- SAYAGO C Aspiration and surgical biopsy *Amer J Roentgenol* 48 (1942) 78
- SHILLER VOLKOVA N N and ARAMOVA K A Cytological punctate examination as a method of breast tumour diagnosis *Vop Onkol* 6 (1960) 54
- SMITH I H, FISHER J H, LOTT J S and THOMSON G H The cytological diagnosis of solid tumours by small needle aspiration and its influence on cancer clinic practice *Canad med Ass J* 80 (1959) 855
- SODERSTROM N Fine needle aspiration biopsy *Almqvist & Wiksell Stockholm* 1966
- STEIN A A Carcinoma in situ of the breast A review *Path Annual* 2 (1967) 47
- STEWART F W The diagnosis of tumors by aspiration *Amer J Path* 9 (1933) 801
- Tumors of the breast *Atlas of tumor pathology* Armed Forces Institute of Pathology Washington D C 1950
- TAILHIEFLR A Diagnostic indications et résultats du traitement du cancer du sein *Bull méd Paris* 71 (1957) 171
- TEMINÉ M R Contribution de la cytologie au diagnostic et à l'étude des tumeurs du sein *Bull Soc Franç Gyn* 26 (1956) 230
- VERHAEGHE M Les moyens modernes de diagnostic des tumeurs du sein *Sem Hop Paris* 39 (1963) 207
- VIAGGIO J A y EQUILA O F La biopsia en el diagnostico del cancer de mama *Pren méd argent* 46 (1959) 534
- ZAJDELA A Valeur et intérêt du diagnostic cytologique dans les tumeurs du sein par ponction Étude de 600 cas confrontés cytologiquement et histologiquement *Arch Anat path* 11 (1963) 85
- (1967) Personal communication
- ZAJICEK J Sampling of cells from human tumours by aspiration biopsy for diagnosis and research *Europ J Cancer* 1 (1965) 253
- FRANZEN S, JAKOBSSON I, RUBIO C and UNGGAARD B Aspiration biopsy of mammary tumors in diagnosis and research A critical review of 2 200 cases *Acta cytol* 11 (1967) 169

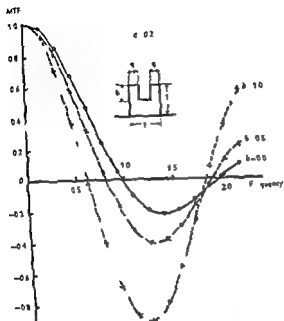


Fig 2 Modulation transfer function of twin peaked symmetric intensity distribution of the focus

where $f(x)$ is a base of function $g_s(x)$ are symmetry components, $g_{as}(x)$ are anti symmetry components and k_0, k_s and k_a are coefficients

Then the Fourier transform is

$$G(f) = k_0 F_0(f) + k_s G_s(f) + k_a G_{as}(f) \quad (1)$$

where $G(f)$ $F_0(f)$ $G_s(f)$ and $G_{as}(f)$ are Fourier transforms of $g(x)$, $f(x)$ $g_s(x)$ and $g_{as}(x)$ respectively and f is a spatial frequency (lines per unit length). The approximation of the rectangular distribution is more convenient to determine than that of the Gaussian. In order to do so the height and width of the focal roentgen intensity distribution are supposed to be of unit length. Parameters b , c and q in Figs 2 to 7 indicate b depth of the valley, c half of the difference between the two peaks (or grade of anti symmetry) and q the width of the peak.

Intensity distribution and its modulation transfer function (MTF)

1 MTF of twin peaked intensity distribution

Let $g(x)$ be the intensity distribution (Fig 2). Its distribution is decomposed into three components that is rectangular distribution of $(1-b)$, symmetric rectangular of qb and anti symmetric rectangular of qc . They are to be linearly

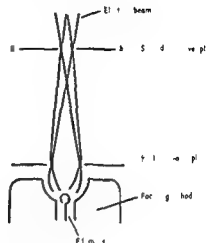


Fig. 1 Schematic track of electrons converged by an electrostatic focusing lens in a conventional roentgen tube

Decomposition of intensity distribution of focal spot into symmetry and anti symmetry components

The roentgen intensity distribution of the focal spot is dependent on the material, coarseness and inclination of the anode, the vibration of the rotating system, the energy of the electrons and the shape of the electron beam (affected by filament voltage, tube voltage and tube current)

In conventional medical roentgen tubes, the electrostatic focusing system focuses thermal electrons from its cathode on a spot of the anode. The thermal electrons from the upper right or left half of the filament are focused on one spot of the anode, and those from the lower right or left half of the filament are focused on the other spot. They cross over each other first in the plane of $a-a$ and a second time in the plane of $b-b$ as a result of the focusing electrostatic field. The former is called the main focal spot and the latter the accessory focal spot (Fig. 1). The second cross over plane of $b-b$ is used in conventional medical roentgen tubes, in which the intensity distribution is twin peaked. Triple or quaternary intensity distributions depend on whether the focal plane is displaced forward or backward from the plane of $b-b$.

In conventional roentgen tubes the single peaked intensity distribution cannot be generally used at the point of roentgen output, either momentarily or continuously. However, it may be obtained in the special roentgen tube of Pierce gun structure which is used in enlargement radiography. All the intensity distributions of the focal spot can be approximately decomposed into rectangular symmetry and anti symmetry components with the center of the roentgen beam. The one dimensional focal roentgen intensity distribution of $g(x)$ is shown as follows

$$g(x) = k_0 f_0(x) + k_1 g_1(x) + k_2 g_2(x)$$

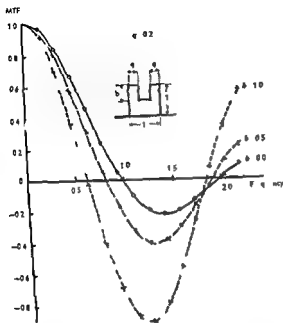


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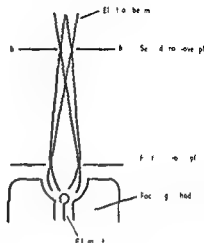


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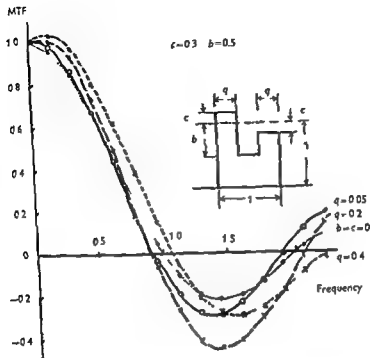


Fig 4 Modulation transfer function of twin peaked anti symmetric intensity distribution of focus

used in television and optical systems. Because roentgen imaging systems contain television and optical systems the overall images and every component in roentgen imaging system should be systematically evaluated from the same standpoint as in the television and optical systems. In television systems the cut-off frequency (f_c) is assumed as the one at the 70.7% decrement of the MTF that is -3 dB (NHK Handbook Japan Broadcasting Corporation Tokyo 1964) in order to compensate for the characteristics of images. If the f_c at the lower amplitude of the MTF that is the broad pass band of the rectangular function is taken the compensation of characteristics will increase the noise and will deteriorate the image quality. In this paper therefore the identical f_c in focal intensity distribution is used as in the television system. The relative cut-off frequency (f_{rc}) is defined as the ratio of the above cut-off frequency of the focus with peaks to that without peaks. The f_{rc} curves of the symmetric twin peaked intensity distribution are obtained

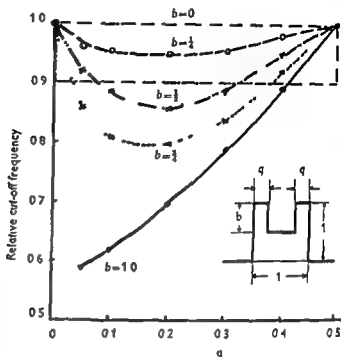


Fig. 3 Distribution parameters of twin peaked symmetric focus and associated cut off frequency

combined with one another, so the above equation is deductively calculated as follows (appendices)

$$\begin{aligned}
 G_{tw}(f) &= (1-b) \frac{\sin \pi f}{\pi f} + 2qb \cos \left\{ 2\pi f(1-q)/2 \right\} \frac{\sin \pi q f}{\pi q f} \\
 &\quad - 2qc \sin \left\{ 2\pi f(1-q)/2 \right\} \frac{\sin \pi q f}{\pi q f} \\
 &= (1-b) \left[F_o(f) + \frac{2q\Gamma(f)}{1-b} \left\{ b \cos \frac{(1-q)a}{c} - \sin \frac{(1-q)a}{c} \right\} \right] \quad (2)
 \end{aligned}$$

where $F_o(f) = (\sin a)/a$, $\Gamma(f) = (\sin qa)/qa$, $a = \pi f$

This parameter c has negative values when the left peak of asymmetric distribution is higher than the right peak and has positive values when the left peak is lower

1—A Symmetric twin peaked intensity distribution If we let $c = 0$ in eq (2), we obtain

$$G_{tw}(f) = (1-b)F_o(f) + 2qF(f)b \cos \frac{(1-q)a}{c} \quad (2)$$

The deeper the valley b of the symmetric twin peaked one in Fig. 2, the more the decrease of MTF in the low frequencies. The MTF is routinely

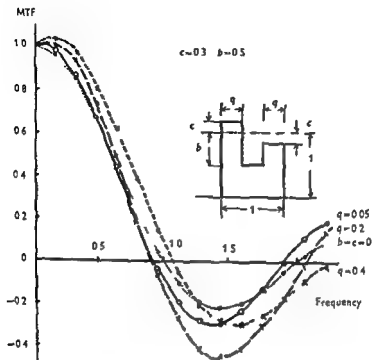


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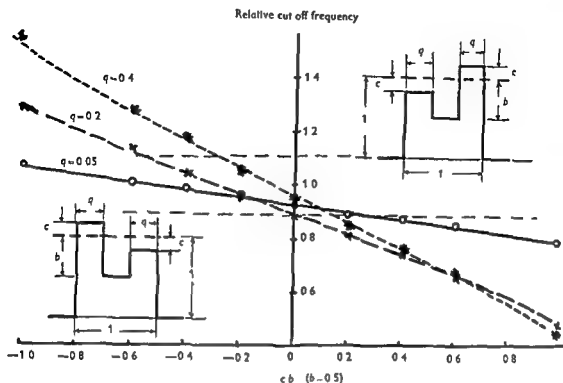


Fig 5 Distribution parameters of twin peaked anti symmetric focus and associated cut off frequency

from their MTF with $b = 0, 1/4, 1/2, 3/4$ and 1.0 . If a 10% decrement of the f_{rc} is to be permitted, the depth b of the valley of the focal spot cannot be more than 0.1 . If $b = 0.5$, the parameter of q should be less than 0.08 , or more than 0.33 . Even if $b > 0.1$, the f_{rc} can be within $\pm 10\%$ variation in $q = 0$ and $q = 0.5$. But, the steep gradients of the f_{rc} (c/b) curves at $q = 0$ and $q = 0.5$ produce a large variation of f_{rc} from a slight change in q . For this reason, the parameter b must be less than 0.4 . If the parameters b and q from the measured focal intensity distribution are not over the dotted lined enclosure (Fig. 3), the decrement of the f_{rc} in the focal spot must be within $\pm 10\%$.

1-B Asymmetric twin peaked intensity distribution It is not always bad in MTF for the deeper depth of valley, not as likely as in the symmetric one. This MTF is asymmetric and is more than 1.0 in the vicinity of $f = 0$. The larger the parameter of c in the higher right peak, the smaller is the f_{rc} . If a 10% decrement of the f_{rc} is to be permitted, there cannot be $q = 0.2$, for the f_{rc} is less than 0.9 ($f > 0$). If $q = 0.05$, $c/b = 0.25$, or $q = 0.4$, $c/b =$

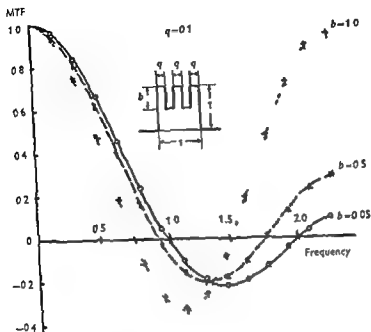


Fig 6 Modulation transfer function of triple peaked symmetric intensity distribution of focus

0.12 the decrement of the f_{re} can be within 10 %. In order to depress the variation of the f_{re} within $\pm 10\%$ the parameters of c/b and q should be within the domain of $f_{re} = 0.9 \sim 1.1$ (Figs 4 and 5)

2 Triple peaked intensity distribution

This distribution has an additional peak in the center of the twin peaked distribution. This is decomposed into four components: rectangular ones of $(1-b)$ and qb , symmetric rectangular of qb and anti-symmetric of qc . Then its Fourier transform $G_T(f)$ is given as follows

$$G_T(f) = (1-b) \left[F_0(f) + \frac{q}{1-b} F(f) \left\{ 2b \cos \frac{(1-q)\alpha}{2} - 2c \sin \frac{(1-q)\alpha}{2} - b \right\} \right] \quad (3)$$

where $F_0(f) = (\sin \alpha)/\alpha$, $F(f) = (\sin qa)/qa$. The parameter α shows the anti-symmetry components and has negative values in the higher left peak of the spot as in the asymmetric twin peaked distribution

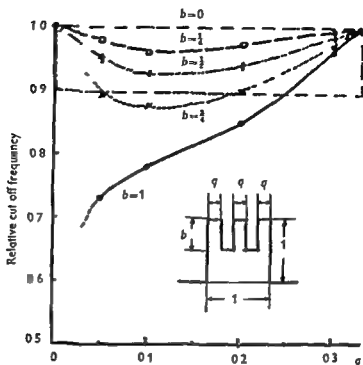


Fig 7 Distribution parameters of triple peaked symmetric focus and associated cut off frequency

2—A *Symmetric triple peaked intensity distribution* has a much better MTF than the twin peaked one. The amplitude at a level higher than the second zero frequency reaches 1.0 (Fig 6). But such high spatial frequencies of the object are not relevant because they cannot be transmitted by a roentgen imaging system with film and fluorescent screens without being obscured by scattering. The decrement of f_{re} is smaller than that of the twin peaked one. In order to enclose the variation of the f_{re} within $\sim 10\%$, the depth of valley b should be less than about 0.6 if possible. Even if $b > 0.6$, the f_{re} may be within $\sim 10\%$ variation in the vicinity of $q = 0$ and $q = 0.5$. Its reason is similar to the symmetric twin peaked focus. The f_{re} of the triple peaked type does not become worse than the twin peaked, even if the valley of the former is deeper than that of the latter (Fig 7).

2—B *Asymmetric triple peaked intensity distribution* has nearly the same MTF as in the rectangular distribution without peak and valley. The amplitude at levels higher than the first zero frequency (spurious resolution) is smaller than the twin peaked one. The asymmetry of this type and the decrement of the f_{re} are smaller than those of the twin peaked one. The selection of q and c/b is standardized as in the asymmetric twin peaked distribution.

The MTF in Fig 2 shows that the single peaked focus of $1 \text{ mm} \times 1 \text{ mm}$, for example has a spurious resolution at a frequency higher than 1 line/mm and that the isolated two-peaked focus has the spurious resolution at a frequency higher than 0.6 lines/mm. The MTF of the asymmetric focus can be more than 1.0 in the vicinity of the origin. It is asymmetric as a whole and has a shifted origin. As is well known in photography, the adjacency effect brings forth such a shift in MTF. Caution, however, should be employed in relation to the asymmetric distribution of a focal spot which shows such a MTF. Even if the decrement of the f_{re} is within permissible limit in the positive frequency domain, some may be out of the limits in negative frequencies. This makes the asymmetric distribution of the focal spot inferior to the symmetric distribution. The single peaked intensity distribution of the focal spot is ideal as regards its MTF and f_{re} . In conventional medical roentgen tubes, however, it is generally twin peaked or triple peaked due to (1) the momentary and continuous heavy load and (2) the high cost of roentgen equipments. In order to make the most effective use of the radiation from the focal spot, its dimensions or the parameters of its intensity distribution should be determined as outlined in this paper. But the decrement percentage of the f_r is determined by the frequency characteristics of the object necessary to diagnose or those of the focus with the permissible load of roentgen tubes.

Appendices

1 *Definition of a base and Fourier transform* As the intensity distribution of the focal spot is approximated by means of rectangular distribution, let $f(x)$ be the following rectangular intensity distribution of the focal spot

$$f(x) = \begin{cases} A & -x_0/2 < x < x/2 \\ 0 & \text{otherwise} \end{cases}$$

then its Fourier transform $F_0(f)$ is

$$F_0(f) = \int_{-\infty}^{\infty} f(x) \exp(-2\pi f x) dx = 4x_0 (\sin \pi x_0 f) / \pi x_0 f$$

where f is a spatial frequency (lines / unit length)

2 *Linearity* Let the intensity distribution be $af(x)$, its Fourier transform is $aF(f)$. And let the intensity distribution be $f_1(x) \pm f_2(x)$, its Fourier transform is $F_1(f) \pm F_2(f)$.

3 *Shift in theorem of Fourier transform* Let $f(x)$ shift x_0 on the x axis and

$$f(x-x_0) = \begin{cases} B & x - D/2 < x < x_0 + D/2 \\ 0 & \text{otherwise} \end{cases}$$

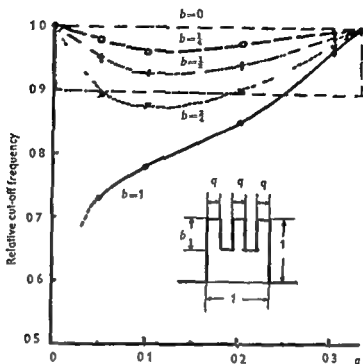


Fig. 7. Distribution parameters of triple peaked symmetric focus and associated cut off frequency

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SIGNIFICANCE OF FOCUS SIZE IN IRRADIATION THERAPY

by

P KLAMM

It is customary in roentgen tube manufacture to reduce the size of the penumbra by means of a small focus. This applies particularly to tubes used in roentgen diagnosis whereas the requirements in this respect are less stringent in roentgen therapy, a small focus is however always considered an advantage as long as it does not excessively restrict the loading of the anode.

Radiation sources of large area dimensions have also been employed, these have mainly been made of radioactive material. Examples are certain tele-radium units (BENNER 1937), radium containing plate applicators and moulds and solutions of radioisotopes. Roentgen sources of large area have been designed for specific purposes: for deep therapy by WITTE, ZIMMER & KESSLER (1939), BARTOW *et coll.* (1949) and by COLOMBO & LENZI (1951); for roentgen television by MOON (1948) and KLAMM (1963); for technical applications by HOFMANN & DIETRICH (1965) and for superficial radiotherapy by KLAMM (1965). The reason why these sources have not been developed is mainly that their practical significance has not been fully realized: thus there has been no economic incentive to those who would have the resources to investigate and manufacture them.

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then its Fourier transform is

$$G(f) = \int_{-\infty}^{\infty} f(x-x_0) \exp\{-2\pi i(x-x_0)f\} dx = \exp(-2\pi i f x_0) F(f)$$

where $F(f) = BD(\sin \pi Df)/\pi Df$

4 Symmetry	Function	Fourier transform
where	$g(x) = f(x+x_0) + f(x-x_0)$ $f(x+x_0) = f(x-x_0)$	$G(f) = 2 \cos 2\pi f x_0 F(f)$
5 Anti symmetry	$g(x) = f(x+x_0) + f(x-x_0)$ $f(x-x_0) = -f(x+x_0)$	$G(f) = -2 \sin 2\pi f x_0 F(f)$
where		

SUMMARY

The intensity distribution of the roentgen focal spot is expanded to symmetry and anti symmetry components on a basis of rectangular function. The parameters of its distribution are standardized by its modulation transfer function and relative cut off frequency. The parameters should be determined by the decrement of relative cut off frequency. The asymmetric focus has an asymmetric modulation transfer function with a shifted origin.

ZUSAMMENFASSUNG

Die Intensitätsverteilung des Röntgenbrennfleckes wird in Symmetrie und Anti Symmetrie Komponente auf rechtwinkliger Funktionsbasis entwickelt. Die Parameter der Intensitätsverteilung werden auf Basis ihrer Modulationsübertragungsfunktion und relativer cut off Frequenz standardisiert und sollen aus der relativen cut off Frequenz bestimmt werden. Die Modulationsverteilungsfunktion des unsymmetrischen Fokus ist unsymmetrisch mit Verschiebung des Origins.

RÉSUMÉ

La distribution spatiale de l'intensité du foyer focale est transformée en composants symétriques et anti symétriques ayant pour base une fonction rectangulaire. Les paramètres de cette distribution sont exprimés par leur fonction de transfert de modulation et la fréquence limite de cut off. Les paramètres peuvent être déterminés par la décroissance de la fréquence limite relative. Le foyer asymétrique a une fonction de transfert de modulation asymétrique avec déplacement de l'origine.

REFERENCES

- NHK Handbook, Japan Broadcasting Corporation, Tokyo 1961
 Recommendations of the ICRUM, NBS Handbook No. 89, National Bureau of Standards, Washington 1963
 Reference data for radio engineering, International Telephone and Telegraph Corporation, Stratford Press Inc., New York 1949

proportionally to the distance so that the area has increased in proportion to the square of the distance

If the side of an irradiated square on the surface of an object O is denoted by a_0 and that of a square area within the object by a_T and the corresponding radiation intensities by I_0 and I_T we have

$$\frac{I_T}{I_0} = \frac{a_0^2}{a_T^2} = \frac{PO^2}{PT^2} \quad (1)$$

from which follows that

$$I_T = I_0 \frac{PO^2}{PT^2}$$

If under otherwise similar conditions the area of the radiation surface F is large (Fig. 1 upper right) it may be theoretically replaced by a point like focus P located farther from the object. If we denote by f the length of the side of the focus F we may write

$$\frac{PO}{PO - FO} = \frac{a}{f} \text{ or } PO = \frac{a}{a - f} FO$$

Hence

$$I_T = I_0 \left(\frac{-f FO}{-f FO + OF} \right)^2$$

or

$$I_T = I_0 \left(\frac{a FO}{a FO + (a - f) OF} \right)^2 \quad (2)$$

The change in radiation intensity with increasing distance has decreased as a result of the increase in the size of the focus. When f equals a I_T is equal to I_0 . This may also be stated as follows:

If the area of the focus is increased until it becomes equal to the area of the object (surface O in Fig. 1 middle left) this implies a shift of the assumed point P to infinity ($PF = \infty$) and hence the ratio of the distances PO and PT is unity

Hence

$$\frac{PO^2}{PT^2} = 1 \text{ and } I_T = I_0$$

The difference in distance would then be of no significance. This is however only speculative. It could be the case in practice if we could delimit the cone of radiation emerging from every point P of the focus F so much that its peak

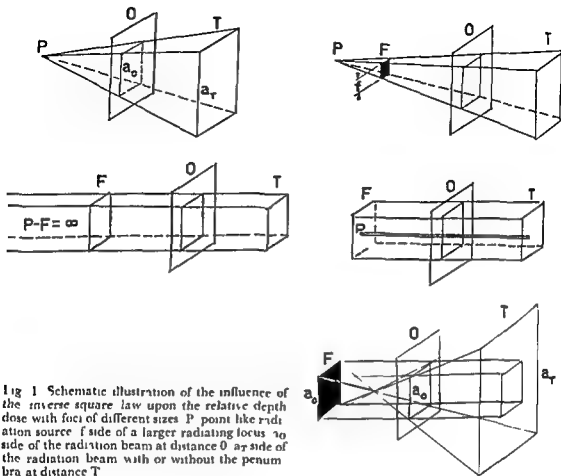


Fig 1 Schematic illustration of the influence of the inverse square law upon the relative depth dose with foci of different sizes P point like radiation source f side of a larger radiating focus a_0 side of the radiation beam at distance 0 a_T side of the radiation beam with or without the penumbra at distance T

The significance of the size of a plane anode in radiotherapy will be considered in this communication. The influence of size when concave and convex anode surfaces are used will be discussed in another publication.

The ratio of the radiation doses within and on the surface of an irradiated object, the so called per cent depth dose, is determined not only by the absorbed and scattered radiation within the material of which the object is composed, but also to a large extent by the focus object distance. When the radiation intensity is measured or calculated, no true point sized radiating focus exists in practice, nor even a point sized measuring instrument. A theoretical 'point concept' is however used in the following to illustrate the dependence of radiation intensity on the focus object distance, on the size of the focus and on other associated factors. Absorption and secondary radiation are disregarded.

The inverse square law is well known (see Fig 1, upper left) the radiation emerging from a point like focus P diminishes with the distance from PO to PT because it spreads over a square surface the side of which has increased

tion from only some of the points of the focus impinges on an area the penumbra outside this field. The intensity of the radiation in the penumbra diminishes as the distance from the centre increases and the source points from which radiation enters the penumbra decrease in number. If we denote by a_T the length of the side of the penumbra area we get

$$\frac{a_T}{a_0} = \frac{\frac{FO}{2} + OT}{\frac{FO}{2}}$$

and

$$a_T^2 = \left(a_0 + 2 \frac{OT}{FO} a_0 \right)^2 \quad (3)$$

The total area exposed to the radiation thus increases with depth and with decreasing distance from the focus to the irradiated field. Especially in contact therapy (FO small) the size of the penumbra and the resulting excessive volume dose already preclude the use of a large focus area without separate collimation of the conical radiation beams.

If as in Fig. 2 a and b the conical beam emerging from each point of the anode is collimated so it becomes relatively limited and a truncated cone C with a peak angle equal to the peak angles of the separate conical beams is used to limit the anode area and irradiated field the following advantages are obtained:

1. The irradiation of the object surface becomes more uniform than in the conditions outlined above. This is particularly so the greater the number of conical beams that fall on a point on the object surface, i.e. the greater the number of foci per unit area of the anode, the larger the peak angles of the conical beams and the larger the focus-object distance. The last condition is not stringent if the first two conditions are fulfilled. Fig. 2 c indicates that the anode surface area must be larger than the irradiated area of the object. If we denote by D_F the diameter of the former, by D_0 the diameter of the latter, by α half the peak angle of the conical beam and by R the radius of the anode surface area irradiating a single point on the object surface then

$$\frac{R}{FO} = \tan \alpha \quad R = FO \tan \alpha$$

and

$$D_F = 2 FO \tan \alpha + D_0 \quad (4)$$

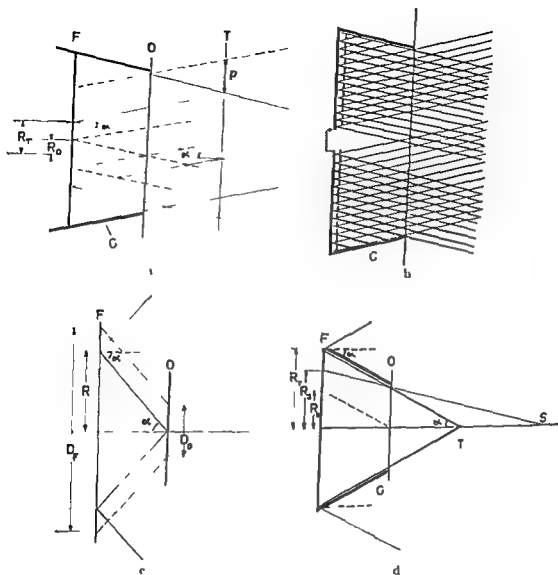


Fig 2 Collimated radiation beams from a roentgen source of large area

angle would be zero (Fig 1, middle right), i.e. if we could arrange so that the radiation emerging from the whole focal surface F were parallel, its divergence according to the inverse square law would not occur.

If, as the other extreme (Fig 1, lower right) the radiation cone is not limited at all (peak angle 180°), a field equal in area to the focus will be formed at distance T and this field will be non homogenous, with a slightly greater intensity of radiation at the centre than elsewhere in the field. This irradiated field is composed of the points struck by radiation from all points of the focus. Radiation

tion from only some of the points of the focus impinges on an area the penumbra outside this field. The intensity of the radiation in the penumbra diminishes as the distance from the centre increases and the source points from which radiation enters the penumbra decrease in number. If we denote by a_T the length of the side of the penumbra area we get

$$\frac{a_T}{a_0} = \frac{\frac{FO}{2} + OT}{\frac{FO}{2}}$$

and

$$a_T^2 = \left(a_0 + 2 \frac{OT}{FO} a_0 \right)^2 \quad (3)$$

The total area exposed to the radiation thus increases with depth and with decreasing distance from the focus to the irradiated field. Especially in contact therapy (FO small) the size of the penumbra and the resulting excessive volume dose already preclude the use of a large focus area without separate collimation of the conical radiation beams.

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$$\frac{R}{FO} = \tan \alpha \quad R = FO \tan \alpha$$

and

$$D_F = 2 FO \tan \alpha + D_0 \quad (4)$$

In practice this limits the magnitude of the peak angle

2 The penumbra can be reduced to moderate size. It is demonstrated in Fig. 2a that when the 'peak angle' of the penumbra is 2α and p is its width at depth OT , then

$$p = 2 \cdot OT \cdot \tan \alpha \quad (5)$$

Also, the reduction of the penumbra requires a suppression of the peak angle

3 From the collimation of the conical beams it follows (Fig. 2a) that radiation falls on a point on the surface of the object O from a smaller area of the anode surface I (from an area of diameter R_O) than on a point at a greater distance T from the object surface (from an area of diameter R_T). The ratio of the circular areas

$$\frac{\pi R_T^2}{\pi R_O^2}$$

may be called the geometric factor GI , the intensity of the radiation increases with distance in proportion to this ratio

$$\frac{R_O}{IO} = \tan \alpha \quad \text{and} \quad \frac{R_T}{IT} = \tan \alpha$$

and hence

$$\frac{R_O}{IO} = \frac{R_T}{IT} \quad \text{and} \quad \frac{R_T}{R_O} = \frac{IT}{IO}$$

regardless of the magnitude of the angle α , and

$$GI = \frac{\pi R_T^2}{\pi R_O^2} = \left(\frac{IT}{IO} \right)^2$$

Superposition of the conical beams thus leads to a geometric increase in the radiation intensity which is proportional to the square of the ratio of IT to IO . On the other hand, eq. (1), divergence of the conical beams produces a converse change in the radiation intensity according to the inverse square law. This decrease in intensity is also proportional to the square of the ratio of these same distances.

These two changes in intensity thus cancel each other, the distances lose their significance, and the intensity diminishes as in parallel radiation only owing to absorption and secondary scattering radiation.

This conclusion is valid up to a certain distance, which depends on the magnitude of the anode area and the peak angle α (Fig. 2d). The following equation gives the relationship between the desired geometric maximum

depth OT the focus object distance FO the radius R of the anode and the peak angle of the collimated conical beams

$$\frac{R_T}{FO + OT} = \tan \alpha \quad (7)$$

As indicated in Fig 2d the geometric factor decreases in value again with increasing depth S ($> T$) because the radius of the anode area that irradiates point S decreases to the value R_s whereas the radius of the anode area that irradiates a point of the object surface remains constant (R_0). Thus

$$\frac{R_s}{R_T - R_0} = \frac{FS}{OS} \text{ and } (F_s = \left(\frac{R_s}{R_0} \right)^2 = \left[\frac{(R_T - R_0) FS}{OS R_0} \right]^2$$

When $R_0 = FO \tan \alpha$ is substituted

$$GF_s = \frac{(R_T - FO \tan \alpha)(FO + OS)}{OS FO \tan \alpha} \quad (8)$$

4 The difficulties associated with the juxtaposition of the two treatment fields are well known either an untreated zone between the fields remains or an excessive dose falls on a zone where the fields are superimposed (HENSCHKE 1943 and others). These disadvantages can be largely eliminated by using the arrangement of several overlapping irradiated fields as shown in Fig 2b

Discussion

As the focus object distance does not influence the relative depth dose when numerous collimated radiation beams are employed it would of course be advantageous to increase the intensity by decreasing the distance. As noted in par 1 p 277 however the irradiation of a surface is more uniform the greater the focus object distance. This must not therefore be shortened too much. It should however be noted that uniform irradiation of the surface of an object is not of prime importance. On the contrary, a method the so called sieve treatment which involves the uneven irradiation of the object surface has long been employed. In sieve therapy the skin may be exposed to a dose of even 20 000 R instead of the customary 3 000 R provided unexposed areas are left on the skin to facilitate recovery from radiation damage. It would hence be desirable when large anode or multifocus tubes are constructed to find a solution that would make it possible to bring an anode fitted with beam collimators in contact with the object surface and in this way to apply short distance roentgen treatment with a sieve. This presupposes that the electrons strike the anode from behind and the produced radiation passes through the

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may be called the geometric factor GF , the intensity of the radiation increases with distance in proportion to this ratio

$$\frac{R_O}{FO} = \tan \alpha \quad \text{and} \quad \frac{R_T}{FT} = \tan \alpha$$

and hence

$$\frac{R_O}{FO} = \frac{R_T}{FT} \quad \text{and} \quad \frac{R_T}{R_O} = \frac{FT}{FO}$$

regardless of the magnitude of the angle α , and

$$GF = \frac{\pi R_T^2}{\pi R_O^2} = \left(\frac{FT}{FO} \right)^2$$

Superposition of the conical beams thus leads to a geometric increase in the radiation intensity which is proportional to the square of the ratio of FT to FO . On the other hand, eq. (1), divergence of the conical beams produces a converse change in the radiation intensity according to the inverse square law. This decrease in intensity is also proportional to the square of the ratio of these same distances.

These two changes in intensity thus cancel each other: the distances lose their significance, and the intensity diminishes as in parallel radiation only owing to absorption and secondary scattering radiation.

This conclusion is valid up to a certain distance, which depends on the magnitude of the anode area and the peak angle α (Fig. 2d). The following equation gives the relationship between the desired geometric maximum

REFERENCES

- BARTON J B BARTON J A and MacLAUGHLIN JR G D Directivity control of X rays USA (1939) Patent 2 638 554 (Application 1949)
- BENNER S The intensity distribution of the new 5 gram bomb of Radiumhemmet Acta radiol 18 (1937) 297
- A method of improving the economy of telerradium treatments Acta radiol 18 (1937) 873
- COLOMBO S and LENZI M Tubo roentgen polianodico Radiol med (Torino) 37 (1931) 411
- HENSCHKE G und HENSCHKE U Zur Technik der Operationsbestrahlung Strahlentherapie 74 (1943) 278
- HOFMANN E G and DIETRICH H CRT X ray generator with beam velocity modulation for equalizing radiation USA (1965) Patent 3 176 137
- KLAMI P Apparatus for roentgenography and television (1963) (Application No 2383 for patent in Finland)
- Anode for a source of roentgen radiation (1965) (Application No 933 for patent in Finland)
- MOON R J Amplification of the fluoroscopic image Amer J Roentgenol 59 (1948) 886
- WITTE ZIMMER und KESSLER Ein neues Röntgenrohr zur Erzeugung konvergenter Strahlenbündel Fortschr Röntgenstr 60 (1939)

anode, and further that the anode be earthed, very thin and effectively cooled. The possibility of constructing a roentgen source of this type, and the advantages attainable by making the anode slightly convex or concave, will be discussed in a forthcoming publication.

When calculations are made to determine the usefulness of a large anode it should be remembered that many factors make it necessary to check the results by means of measurements in phantoms. The average thickness of matter penetrated by the radiation is slightly greater than the perpendicular distance from the surface to the depth in question. The outline of every radiation beam is also rendered indistinct by a focus of large area, even collimators made of heavy metal transmit some radiation and secondary radiation is produced at their edges, especially when high energy radiation is employed. These factors are under investigation.

It would be interesting to know whether the geometric factors discussed are of value with very high energy photon sources, such as the betatron and the linear accelerator. The radiation beams of these are narrow ($\sim 10^\circ$) and no collimator would be required when targets of large area are irradiated by moving the electron beam. When irradiation takes place with an energy source such as radium or cobalt 60, collimation would hardly be possible in practice owing to the thickness that would be required for the wall of the collimator.

SUMMARY

The possibilities of using radiation sources with anodes of large area in radiation therapy are explored. It is concluded that the focus object distance can be greatly reduced without influencing the per cent depth dose if the radiation is divided into a number of collimated beams.

ZUSAMMENFASSUNG

Die Anwendbarkeit in der Strahlentherapie von Strahlenquellen mit grossen Anodenoberflächen wird erörtert und es wird festgestellt dass ohne Einwirkung auf die relative Tiefendosis der Fokus Hautabstand stark reduziert werden kann wenn die Bestrahlung in mehreren Strahlenbündeln verteilt wird.

RÉSUMÉ

L'auteur a étudié la possibilité d'utiliser des sources de radiation ayant des anodes de grande surface en radiothérapie. Il conclut qu'on peut réduire beaucoup la distance foyer objet sans influencer sur le pourcentage des doses en profondeur à condition que le rayonnement soit divisé en plusieurs faisceaux collimatés.

REFERENCES

- BARTON J H, BARTON J A and MACLAUGHLIN JR G D Directivity control of X rays USA (1939) Patent 2 638 554 (Application 1949)
- BENNER S The intensity distribution of the new 5 gram bomb of Radiumhemmet Acta radiol 18 (1937) 297
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- HENSCHKE G und HENSCHKE U Zur Technik der Operationsbestrahlung Strahlentherapie 74 (1943) 298
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ROENTGEN STAND FOR FIELD POSITIONING IN HIGH ENERGY RADIOTHERAPY

by

BO JUNG, BORJE LARSSON, BENGT ROSENCRÖN, KAY STÅHL
and WILHELM WRETHIND

The application of high energy radiation in external therapy has emphasized the importance of accuracy in the dose planning. The experience is that roentgenography with diagnostic stands is generally not adequate as a basis for the positioning of the radiation fields. This is mainly due to the fact that the actual projections and the proper focus to tumour distances are not achieved and there is also the trivial problem of having the patient positioned identically as on the therapy couch.

The high energy beams themselves are not suited for radiography due to the low contrast of the image. JOHNS & CUMMINGHAM (1959) introduced an auxiliary diagnostic roentgen tube in the therapy head, but such a system does not allow the therapy equipment to be fully utilized for irradiation. In recent years the construction of roentgen stands especially designed for field positioning and tumour localization has been undertaken at several radiotherapeutic centres (cf below). This paper describes such a project. It has resulted in two, almost identical equipments which are now in use in Uppsala and in Gothenburg.

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A The therapeutic procedure and the positioning stand

The construction principles and the use of a localization stand is probably best discussed with reference to the envisaged treatment procedure. This is given by the following scheme:

I Localize the outlines of tumour and internal organs in one or several parallel projections; mark the projections of points of interest on the skin of the patient; measure the outline of the patient and make with the aid of the skin marks accurate drawings of the desired cross-sections of the patient with tumour and internal organs indicated at proper positions.

II Select treatment technique from information on position of tumour and critical organs as well as on possible earlier radiotherapy.

III Calculate dose distribution.

IV Simulate selected treatment fields; check that the treatment fields are in correct position in relation to the target volume and the critical organs; mark on the skin of the patient entrance (and exit) points of central beam axes and entrance (and exit) fields.

V Adjust patient to therapy beam by aid of skin marks; irradiate.

From this scheme the following conclusions can be drawn regarding the specifications which should be met by the localization stand:

1 Any projection which can be achieved with the therapeutic stands should be obtained. In practice this condition prescribes a full 4 π rotation with respect to the patient. The movements available in the patient's couch decrease the requirements on the localization stand; however:

2 The focus-isocentrum distances should be variable and match those available in the therapeutic apparatus.

3 The roentgen image should be transmitted by an image intensifier closed circuit TV system. The image plane should be variable with respect to the patient so that the best image quality is secured. Provisions for exposure of documentary roentgenograms should be made.

4 The patient's couch, including fixation apparatus, rolls, etc. should match closely the one used at the therapeutic apparatus. The movements of the couches do not necessarily have to be identical; however:

5 If the patient's posture can be accurately related to some external coordinate system it is possible to transfer the coordinates of the target volume at the localization stand to the therapeutic unit. In this case the coordinate system should parallel exactly that of the therapy unit. Usually transfer of patient coordinates from the localization stand to the therapy unit prescribes the use of castings and fixture or special stereotaxic apparatus.

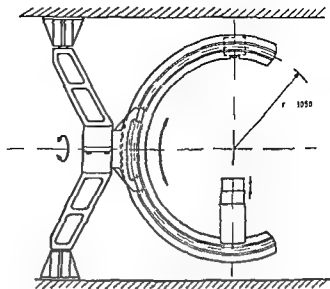


Fig 1 Early version of the localization stand employing a sliding and rotatory arc. A 1:100 model was tested for mechanical and practical properties. The advantages of this construction over the finally adopted principle are outweighed by the much higher manufacturing costs.

6 When moving field therapy is important, the movements of the localization stand and the therapy units should match each other closely, also with respect to accuracy.

7 The required accuracy depends critically on the intended use of the roentgen stand. For localization and field control the demands are moderate, while for simulation of moving field therapy they are much higher. If the faculty of accurate transfer of coordinates from the localization stand to the therapy equipment is requested the specifications for accuracy are even higher.

Two approaches of marked different complexity have been followed in the development of roentgen stands for field positioning and simulation. In the first the movement of the roentgen tube is restricted to a rotation around one axis; in the other the roentgen tube (and image plane) has so many degrees of freedom that complete simulation of sophisticated therapy equipment is attained. Examples of the first type are the constructions of BECKER, WERNER & WITZEL (1955), CATTON (1957), FARMER, FOWLER & HACCITH (1963), HEINZEL & WICHMANN (1963) and GREENE, NELSON & GIBB (1964) while NETTELAND (1967) and MADSEN (1967) have constructed apparatus of much higher flexibility.

No detailed report of clinical experience is available for any of the constructions and it is hard to judge the importance of the various constructional features. Most probably, the routine uses of the different stands will vary considerably from clinic to clinic depending on the local praxis and the therapy units at hand.

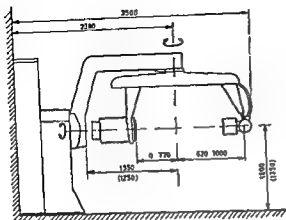


Fig. 2 Localization stand with a rotatory arc on a rotatory arm. This construction was finally adopted (The measures are in millimeters)

B Constructional

In a first model construction a combination of a rotation axis and a semi-circular sliding action was tried (Fig. 1). This construction may have some advantages with respect to the accessibility around the patient but was abandoned for technical and economical reasons.

The final apparatus in Figs. 2 and 3 employs a system of two intersecting orthogonal rotating axes and is related in principle to a diagnostic stand used in neuroradiology (FREDZELL & LINDGREN 1960). In conventional clinical praxis and when the patient's couch is mounted isocentrically one of the axes can be omitted but many therapy units have movements around two axes and a couch which is not mounted isocentrically. This was the case with one cobalt unit and the betatron in Gothenburg. Also as a localization stand for radiotherapy with high energy protons as in Uppsala both axes are necessary, since the direction of the proton beam is fixed in the room. With this construction, projections with axes coincident with and perpendicular to the axes of the foreseen therapeutic beams are obtained without movement of the patient. The extra complication of two axes is technically counterweighed at least partially by the fact that the movable arms carrying the roentgen source and the image amplifier can be made shorter without loss of accessibility to the patient. The focus-isocentrum and image plane isocentrum distances are both variable. Further degrees of freedom were considered unnecessary.

The two rotary movements are driven by variable speed DC motors which also serve as brakes. The translational movements of the roentgen tube and image amplifier are driven by a motor with constant speed. In Uppsala the roentgen

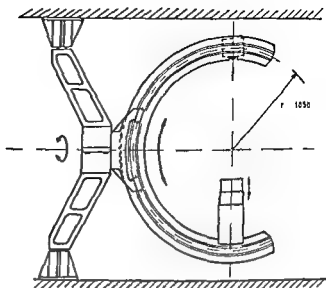


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D Practical experience

The Uppsala equipment now in use since several years has met the expectation, very well. It is used to align the patients for proton therapy and the most common projections are antiparallel and perpendicular to the beam. The severe spatial limitations at the narrow irradiation site further accentuated by the necessary equipment for the proton beam has posed some access problems. The experience gathered in Gothenburg over two years and from about 1500 patients is of more general interest and is discussed in a paper subsequently to be published (JOHANSSON, ROSENGREN & TJERNBERG). In routine work the equipment allows the patient's preparation for irradiation to be shortened by one day.

Acknowledgements

The construction of localization stands for use in high energy radiotherapy has been the object of a discussion group formed within the Nordic Association of Radiophysicists. We thank the members of the group and colleagues at our institutes for personal communications and practical advice. The work was supported by Knut and Alice Wallenberg's Stiftelse, the Swedish Medical Research Council and Elema Schöander.

SUMMARY

A unit for use in dose planning and field localization with a roentgen source and an image amplifier mechanically coupled together by an arc is described. The arc can be rotated isocentrically around its perpendicular axis. The focus isocentrum and image plane isocentrum distances are both variable.

ZUSAMMENFASSUNG

Ein Gerät zur Dosisplanung und Lokalisierung der Bestrahlungsfelder in dem die Röntgenquelle und ein Bildverstärker durch einen Bogen mechanisch miteinander verbunden sind wird beschrieben. Der Bogen kann isozentral um zwei senkrechte Achsen rotiert werden. Die Abstände Fokus Isozentrum und Bildebene Isozentrum sind beide variabel.

RÉSUMÉ

Les auteurs décrivent un équipement destiné à établir le plan d'irradiation et la localisation des champs au moyen d'une source de rayons X et d'un amplificateur d'image réunis par un arc. L'arc peut tourner autour de deux axes perpendiculaires. On peut faire varier la distance du foyer au centre de rotation et la distance du plan image au centre de rotation.

Fig 3 Localization stand at the radiotherapeutic clinic in Gothenburg. The stand is now in routine use for localization and simulation during the preparatory procedures for radiotherapy with gamma and high energy roentgen rays.



collimator is of conventional design (Siemens No 501 423), whereas in Gothenburg a special device which simulates the collimator systems of the therapy units has been used. Four parallel bars outlining the margin of the field can be moved simultaneously in antiparallel directions and both pairs can be rotated together around the central axis of the roentgen beam.

The image amplifiers are of Siemens make (10' in Uppsala, 9" in Gothenburg) coupled to Siemens closed circuit IV links, whereas the roentgen sources are a Philips type PH 125/180 (max 125 kVp) in Uppsala and an Elekta Schöander type Triplex Optimatec 723 (max 125 kVp) in Gothenburg. The movement of the roentgen head is restricted to a little more than a hemisphere due to the inflexibility of the cabling for the roentgen and image intensifier equipments.

The patient's couch is mounted isocentrically at both places. It is important that the mounting of the couch does not interfere with the movements of the roentgen tube and image intensifier.

C Precision

The Uppsala machine is the prototype and its isocentricity defined as the minimum volume crossed by a fixed line between the roentgen focus and the image plane for all settings of the equipment is of the order of $4\text{ mm} \times 4\text{ mm} \times 8\text{ mm}$, the deviation being largest for horizontal settings of the arm. The arm of the Gothenburg apparatus is 10 cm longer but has a more sturdy construction and the volume defined earlier is in this case $3\text{ mm} \times 5\text{ mm} \times 6\text{ mm}$.

VASCULAR INSUFFICIENCY IN PREMALIGNANT AND PRE INVASIVE SQUAMOUS EPITHELIUM

by

E RUBINSTEIN

The blood supply as well as the oxygen pressure are of great importance in malignant tumours treated by modern radiotherapy adequate circulation in the tumour tissues is also essential for positive therapeutic results in chemotherapy There is good reason to assume that the growing rate of many malignant tumours is much higher in the epithelium than in the underlying capillary bed This at an early stage often results in hypoxia leading finally to necrosis

Early investigations The importance of vascularization in the treatment of malignant tumours has been emphasized by CRAMER (1934) and MOTTRAM (1935) THOMLINSON & GRAY (1955) and GRAY (1961) studied the clinical application of the oxygen problem and correlated the morphologic and physiologic results Several papers on the morphology of the terminal capillary bed in the squamous epithelium present various correlations of the vascularization in early as well as advanced cases of carcinoma The favourable anatomic site of the portio vaginalis uteri has rendered it popular for investigation and valuable results have already been obtained (SUOHARA 1958 KOS et coll 1960 ZINSER & ROSENBAUER 1960 KOLLER 1963 KOS & LANE 1963 KOLSTAD 1964 1965 RUBINSTEIN 1968)

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REFERENCES

- BECKER J WERNER K and WEITZEL G Lokalisations und Einstelltechnik bei dem 15 MeV Siemens Betatron Strahlentherapie 97 (1955), 202
- CATTON G E Localization of tumours for cobalt 60 circumaxial rotation J Can Ass Radiol 11 (1957) 36
- FARMER F T FOWLER J F and HAGGITH J W Megavoltage treatment planning and the use of xeroradiography Brit J Radiol 36 (1963) 426
- FREDZELL C and LINDGREN E Mimer Acta radiol 53 (1960) 209
- GREENE D NELSON K A and GIBB R The use of a linear accelerator simulator in radio therapy Brit J Radiol 37 (1964), 394
- HEINZEL F and WICHMANN H Some remarks about localization and positioning technique in telecobalt therapy Medica mundi 9 (1963) 5
- JOHANSSON J ROSENGREN B and TJERNBERG H Clinical applications of a field positioning and simulating stand To be published in ~~Amer J Ther Phys Biol~~ Ther Phys Biol
- JOHNS H E and CUNNINGHAM J R A precision cobalt 60 unit for fixed field and rotation therapy Amer J Roentgenol 81 (1959) 4
- MADSEN C H Private communication (1967)
- NETTELAND O Private communication (1967)

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The blood supply as well as the oxygen pressure are of great importance in malignant tumours treated by modern radiotherapy. Adequate circulation in the tumour tissues is also essential for positive therapeutic results in chemotherapy. There is good reason to assume that the growing rate of many malignant tumours is much higher in the epithelium than in the underlying capillary bed. This at an early stage often results in hypoxia leading finally to necrosis.

Early investigations The importance of vascularization in the treatment of malignant tumours has been emphasized by CRAMER (1934) and MOTTRAM (1935). THOMLINSON & GRAY (1955) and GRAY (1961) studied the clinical application of the oxygen problem and correlated the morphologic and physiologic results. Several papers on the morphology of the terminal capillary bed in the squamous epithelium present various correlations of the vascularization in early as well as advanced cases of carcinoma. The favourable anatomic site of the portio vaginalis uteri has rendered it popular for investigation and valuable results have already been obtained (SUGIHARA 1958, KOS et coll 1960, ZINER & ROSENBAUER 1960, KOLIER 1963, KOS & LANE 1963, KOLSTAD 1964, 1965, RUBINSTEIN 1968).

Submitted for publication 11 January 1968

These investigations indicate that the vascularization in the pathologically transformed squamous epithelium is different from that in normal epithelium. The degree of vascular insufficiency in malignant tumours depends finally on the capillary circulation within the growth. Even if oxygen therapy makes it possible in many cases to raise the partial oxygen pressure in the tumour and decrease the hypoxia, it is still difficult to achieve a uniform and general improvement of the circulation in the tissues. This applies particularly to tumours with large intercapillary spaces, the increase in the capillary oxygen pressure obtained by oxygen inhalation is not even sufficient to increase the oxygen pressure in intercapillary tumour tissues (THOMINSON & GRAY 1955, GRAY 1961). Information concerning the vascular conditions in the entire epithelium, and on the hypoxia that may occur in the intercapillary tissues is therefore of particular interest.

The author has developed an optical method that offers authentic registration of the morphologic features of the epithelium and the underlying capillary bed (1956, 1967). The more marked the growth of the epithelium is, the coarser appears the capillary bed, and, at the same time, the greater is anemia. The present paper deals with further development of this method, by means of which it is possible practically to study eventual correlations between the vascular insufficiency of the epithelium and the precancerous and pre-invasive epithelial appearances.

Material. This is based on the investigation of 164 women in ages from 17 to 77 years. The total number of squamous epithelial areas in the portio uteri investigated was 364. Each portio was examined first by means of a cytologic smear and then through a colposcope, in several cases with direct photographic recording of selected areas. All the 364 specimens were examined histologically. The findings were as follows:

		<i>Number of specimens</i>
Inflammation only		185
Dysplasia		
of low degree	71	
of high degree	49	119
Carcinoma in situ		60

Author's method. A self-retaining speculum having been introduced into the vagina, the ectocervix is inspected and a cytologic smear taken from the vagina and the posterior vaginal fornix. The portio is examined through the colposcope. The mucous secretions are removed with physiologic saline and acetic acid 2%.



Macroscopic appearance of squamous epithelium hyperemic (top) hyperic of low degree (middle) and hyperic of high degree (bottom view)

is applied by soft gauze pressed on the epithelium, the epithelium is thus fixed *in vivo*. The cytologic smear is stained by the Papanicolaou original method (PAPANICOLAOU & TRAUT 1943). The histologic specimens are fixed in formalin, embedded in paraffin, and stained by the van Gieson and periodic acid Schiff methods.

The use of acetic acid 2% plays the main role in this procedure. HINSFELMANN (1938) pointed out the advantage of acetic acid 2% to 4% in so called enlargement colposcopy. GANSE (1958) and KOLSTAD (JOHANNISSON *et coll.* 1966) have been critical of the use of astringent solutions in the study of epithelium *in vivo*. They have pointed out that fine capillary networks disappear and coarse networks become coarser after such fixation. Taking the epithelium as a whole, the changes in the morphologic appearances produced by the acetic acid seem to me advantageous, however (RUBINSTEIN 1966, 1967). Fine normal capillaries are to some extent blurred out, whereas the coarse and pathologic capillaries appear more clearly. The contrasts thus become more accentuated, a fact that makes the evaluation easier. Numerous finer terminal capillaries appear clearly first after fixation, to disappear or to be blurred out again in 2 to 3 minutes. Further fixation causes the capillaries to reappear.

Normal vascular appearances. The epithelial regrowth in histologically normal regions may be examined by a colposcope, this takes place in the so called transformation zone that lies between the cylindrical and the squamous epithelium and consists of a narrow circular zone bounded on the two sides by indistinct borders. The characteristic structure of the cylindrical epithelium may be observed under the thin squamous epithelium. A red epithelial zone is first apparent but fixation causes the thin squamous epithelium to appear, and the underlying ectopic cylindric epithelium will be visible. The terminal capillaries consist of fine linear and network capillaries or fine circular and spider capillaries. Immediately after fixation the terminal capillaries are blurred out, and no atypical capillaries are visible.

Hyperemia. The hyperemic squamous epithelium in the portio is characteristic in appearance, the thin and transparent epithelium is intensely red and richly vascularized. When fixed *in vivo* the underlying capillary bed emerges as small and fine punctuations among network and circular capillaries. These punctuations often appear very clearly just after fixation, and lose their colour after some minutes. The epithelium as a whole is richly vascularized and intensely red in colour, it is always thin and elastic.

Hypemia. The hypemic squamous epithelium has a clear tendency towards proliferation, with marked variations in colour and thickness. The capillaries are

Table

Vascularization and histologic findings in 364 epithelial specimens

	Number of specimens	Inflammation only	Dysplasias		Carcinoma in situ
			Low degree	High degree	
Normal vascularization	90	76	13	1	—
Hyperemic	21	11	9	1	—
Hypemic	253	98	49	46	60

coarse and variable in appearance coarse punctuations alternating with mosaic capillary zones the capillaries are dilated Due to poor vascularization and circulation the epithelium has an anemic grey or greyish white colour and keratinization may occur Advanced epithelial proliferation keratinization and coarse capillaries may be associated with a high degree of hypemia The intercapillary distances are increased

Results and Discussion

No epithelial area with normal capillary characteristics and vascularization presented histologic signs of carcinoma in situ There was one case of high-degree dysplasia (1.5%) among the 90 cases in this group The number of low degree dysplasias were 13 (14.5%)

No hyperemic epithelial area had evidence of carcinoma in situ High degree dysplasia was present in one of the 21 cases in this group (5%) and low degree dysplasia was present in nine of the cases (43%)

All the 60 cases of carcinoma in situ were found in the hypemic epithelium areas A similar hypemic vascularization was present in 96% (46/48) of the high degree dysplasias and in 69% (49/71) of the low degree dysplasias in this group

The existence of histologically benign inflammatory epithelium in all the three groups of vascularization proves that the vascular appearance of the epithelium is not a decisive criterion of malignancy

Valuable information on the circulation in the tumour is obtained by complementing the morphologic examination of the capillary beds with measurements of the oxygen pressure in the tumour and study of the variations before and during therapy Such measurements generally confirm the inadequate vascularization and hypoxia of a malignant tumour

Experiments in animals have indicated (THOMLINSON & GRAY 1955, and GRAY 1961) that the effect obtained for instance by oxygen inhalation does not include the more central parts of the tumour. Complete anoxia, in spite of the partial oxygen pressure of the arterial blood, may exist at a distance of 0.2 mm from the terminal capillaries. These observations are of paramount practical value because they offer an explanation of the fact that for many tumours oxygen therapy has no effect. HOLSTAD (1964, 1965) proved that large intercapillary distances (>0.25 mm) produce a characteristic sign in malignant, pre-invasive epithelium. Even dysplastic epithelium often displays similar vascular characteristics.

The epithelium as a whole may also be examined in order to obtain some idea concerning the circulation in precancerous or pre-invasive epithelial change (RUBINSTEIN 1966, 1967). Then, not only the morphologic features of the capillary bed but also the colour, tendency to proliferation and the superficial structure of the epithelium are examined. Typical findings indicating early malignant epithelial changes are marked vascular insufficiency and anemia. The question of correlation between this vascular insufficiency and the degree of epithelial malignancy is of considerable importance. The capillary changes may offer important information on the neoplastic activity of the epithelium but cannot be used as a direct measure of malignancy. The whole epithelium must be examined. Dysplasia and carcinoma in situ are histologic terms implying that a careful study of the various epithelial layers has been made, but has not necessarily included the underlying capillary bed.

The various vascular appearances are optical images of the capillaries of the stromal papillae caused by the mutual activity between these capillaries and the finger-like epithelial buds.

The present material proves that the precancerous and pre-invasive squamous epithelia are usually hypemic. Furthermore, a hypemic epithelial area need not necessarily be malignant. Malignant tumours are dynamical, kaleidoscopic growths. The appearance of the epithelium is one coordinate in the whole system, while the appearance of the capillaries is another. Only occasionally do these two run parallel.

SUMMARY

Characteristic hypemia was evident in precancerous and pre-invasive tissue of the portio vaginalis uteri examined in vivo in a material of 164 subjects. Changes in the epithelial appearance are correlated with vascular insufficiency of the epithelium. The significance of the findings is discussed.

ZUSAMMENFASSUNG

Bei in vivo Untersuchung der Portio vaginalis uteri in 164 Fällen wurde festgestellt, dass eine stark verminderte Gefäßversorgung ein charakteristisches Zeichen von precancerösem Gewebe war. Korrelation zwischen dem Aussehen des Epithels und der geringen Blutzufuhr zum Epithel wurde konstatiert. Die Bedeutung dieser Befunde wird erörtert.

RÉSUMÉ

Sur une série de 164 malades examinées in vivo l'auteur a trouvé une diminution caractéristique de la circulation dans les tissus précancéreux et pré invasifs du col de l'utérus. Il a établi une corrélation entre les aspects épithéliaux et l'insuffisance vasculaire de l'épithélium. L'intérêt de cette constatation est étudié.

REFERENCES

- CRAMER W. 11th Sci. Rep. Imperial Cancer Research Fund (1931) 177
- GANSE R. Das normale und pathologische Gefäßbild der Portio vaginalis uteri. Akademie Verlag, Berlin 1958
- GRAY L. H. Radiobiologic basis of oxygen as a modifying factor in radiation therapy. *Amer. J. Roentgenol.* 85 (1961) 803
- HINELMANN H. Die Essigsäureprobe ein Bestandteil der erweiterten Kolposkopie. *Dtsch. med. Wschr.* 64 (1938) 40
- JOHANSSON E., KOLSTAD P. and SÖDERBERG G. Cytologic, vascular and histologic patterns of dysplasia, carcinoma in situ and early invasive carcinoma of the cervix. *Acta radiol.* (1966) Suppl. No. 258
- KOLLER O. The vascular patterns of the uterine cervix. Universitetsforlaget, Oslo 1963
- KOLSTAD P. Vascularization, oxygen tension and radio-sensitivity in cancer of the cervix. Universitetsforlaget, Oslo 1964
- The development of the vascular bed in tumours as seen in squamous cell carcinoma of the cervix uteri. *Brit. J. Radiol.* 38 (1965) 216
- KOS J. and LANE V. Die Architektonik der terminalen Blutgefäße an der Cervix uteri. *Kolposkop. zytol. Studien*, Heft 9 1963. Thieme
- MIKOLAS V. L. and LANE V. Das Bild des terminalen Blutgefäßnetzes auf der karzinomatösen Cervix uteri. *Arch. Gynak.* 82 (1960) 1487
- MORTFAN J. C. On alteration in sensitivity of cells towards radiation produced by cold and by anaerobiosis. *Brit. J. Radiol.* 8 (1935) 32
- PAPANICOLAOU G. N. and TRAUT H. F. Diagnosis of uterine carcinoma by the vaginal smear. Commonwealth Foundation, New York 1943
- RUBINSTEIN E. On the proliferation of the squamous epithelium on the portio vaginalis uteri. Dissertation, Helsinki 1966
- Kolposkopins värde som klinisk undersökningsmetod. (In Swedish.) *Svenska Lak. Tidn.* 61 (1967) 1345
- Vascular insufficiency in malignant tumours: radiotherapeutic aspects. (In Swedish.) *Nord. Med.* 79 (1968) 117

- SUGIARA E. The morphological study of blood vessels in cervical carcinoma. *Acta Med Okayama* 12 (1958) 261
- THOMLINSON R. H. and GRAY L. H. The histological structure of some human lung cancers and the possible implications for radiotherapy. *Brit J Cancer* 9 (1955) 539
- ZINER H. K. und ROSLBAUER K. H. Untersuchungen über die Angioarchitektur der normalen und pathologisch veränderten Cervix uteri. I. *Arch Gynak* 194 (1960) 73
- Untersuchungen an der geschwänzten Cervix uteri. II. *Geburish u Frauenheilk* 70 (1960), 658

EVALUATION OF EXPERIMENTAL IRRADIATION FRACTIONATION WITH THE SINGLE HIT, MULTI TARGET MODEL

by

IRJA SPRING and PETER HOLMBERG

All theoretical models developed for indicating the dose response curve in irradiation of cells are based upon the interaction of ionizing radiation with the cells (FORSELL 1924 WARREN 1957, HIGGINS 1958). The one most commonly used is the single hit multi target model (ZIMMER 1961). This model as represented by formula (1) is often referred to as a multi hit model although the equation does in fact correspond to a multi target model in which it is assumed that the cells have several targets each requiring one hit for inactivation. This particular model was employed in this study. The multi hit single target model (OLIVER & SHEPSTONE 1964) and the kinetic model (DIENES 1966) are also of value. Some kind of treatment fractionation is usually applied in radiotherapy and consequently the function describing the total dose producing a certain effect for different numbers of fractions is of importance to radiotherapists. Surveys of experimental findings concerned with the change in the total dose with fractionated treatment have been published (see FOWLER & STERN 1963, WOOTTON 1966). These findings were obtained in animal in vivo and in vitro experiments.

FOWLER (1965) presented two ways of considering the change in the total dose with the overall time used. One way (A) was derived by replottting clinical data and results from normal tissues of experimental animals, it corresponded to a high extrapolation number and a survival curve slope that continued to increase with dose. The other way (B) was by calculation from a simple cell survival model, assuming a single hit, multi target model with an extrapolation number of 2.8, and a 37 % dose slope $D_0 = 140$ rad. He concluded that the two predictions may be regarded as limiting values between which the empirical answers might be expected to lie, although he preferred experimental results derived from (A).

If a start is made from the assumption that different types of radiosensitive and 'radioresistant' cells exist at the beginning of the irradiation, or from the assumption that the cells change to more 'radioresistant' cells after several irradiations, a change is to be expected in the extrapolation number and in the 37 % dose slope during fractionation treatment. The findings reported in this paper do not include cell repopulation during the time of treatment.

The purpose of this study was to compare the results determined experimentally and reported by FOWLER (1965), and indicating the change in the total dose taken against the number of fractions, with corresponding results derived by means of the single hit, multi target model. It was hoped that the use of a criterion in respect of the closeness of the fit of the experimental and theoretical results, together with a suitable assumption concerning a variation of the values of the extrapolation number and the 37 % dose slope, would permit a better description of the experimental results.

The single hit, multi target model The fact that on the absorption of radiation, the events (hits) are statistically distributed and mutually independent means that Poisson's law is relevant. If it is assumed that the cells consist of m targets, each of which must receive one hit to make the cell react, i.e. lose its reproductive integrity, the following formula is valid:

$$S = 1 - (1 - e^{-D/D_0})^m \quad (1)$$

This formula gives the cell survival curve in dealing with the single hit, multi target model.

S is the proportion of the cell population which survives the dose D (rad). D_0 (rad) is the 37 % dose slope, i.e. the dose required to reduce the survival proportion to 37 % of its initial value on the straight region of the logarithmic survival curve. The extrapolation number m may be thought of as the average number of targets (sensitive sites) in the cell but should rather be regarded as a mathematical parameter with no morphologic or biochemical significance.

It has been found that this formula provides a good description of the survival of a cell population given a single radiation dose. Usually m lies between 2 and 10 and D_0 between 100 and 180 rad for oxygenated cells. For anoxic cells D_0 increases to about 400 rad.

Fractionation For small values of D the shoulder of the survival curve plays an important role. In fractionation radiotherapy accordingly the total dose has to be increased for attainment of the same survival proportion as in one treatment; this depends upon the reduction in the efficiency of irradiation with small doses. The final surviving proportion S_N after N treatments may be calculated from the following formula:

$$S_N = \{1 - (1 - e^{-D/D_0})^m\}^N \quad (2)$$

assuming that parameters D_0 and m do not change during the fractionated treatment. N is the number of fractions and consequently D/N the dose per fraction.

The experimental values considered by FOWLER (1965) give the total doses D for different numbers of fractions 1, 2, ..., N . If the doses given are used, then the same survival proportion S_N will be derived regardless of the number of fractions; i.e. $S_1 = S_2 = \dots = S_N$ respectively. If the experimentally determined values of D corresponding to different numbers of fractions are introduced into formula (2) a series of S_N are obtained, all of which should be equal if the model describes the process perfectly, and the proper values for m and D_0 have been chosen. This is not the case in practice, where a set of different S_N values results. The values for these that best fit the experimental results are determinable by varying m and D_0 . A general criterion called the relative closeness of fit has been employed; this is indicated by Q and defined as follows:

$$Q = \frac{1}{N} \sum \{S_N - \bar{S}\}^2 / (k-2) \quad (3)$$

\bar{S} is the mean value of the S_N values obtained, S_N the survival proportion corresponding to N fractions and $(k-2)$ the degree of freedom, where k is the number of experimental values.

The smallest value of Q exhibits the best fit between the experimental and theoretical results. The results of calculation are presented below.

Cell population with two different cell types A model of a cell population comprising two different types of cells, radiosensitive and radioresistant, was also employed. The following formula was used:

$$S_N = x \{1 - (1 - e^{-D_1/D})^m\}^N + (1-x) \{1 - (1 - e^{-D_2/D})^{m_2}\}^N \quad (4)$$

x is the proportion of 'radiosensitive' cells at the beginning of the irradiation. Thus, $(1-x)$ is the proportion of the 'radioresistant' cells, D the total dose, N the number of fractions and D/N the dose per fraction as defined earlier. D_1 and D_2 are the 37 % dose slopes, and m_1 and m_2 the extrapolation numbers of the 'radiosensitive' and 'radioresistant' cells, respectively.

The criterion for closeness of fit given in formula (3) was also applied in the calculation with formula (4).

Cell population with varying parameters A further model, in which parameters m and D_0 change during the fractionated treatment, was also studied. The formula corresponds to a cell population which changes to a more 'radioresistant' one with an increasing number of fractions.

$$S_N = \{1 - (1 - e^{-D_1/D})^m\}^N \quad (5)$$

where

$$A = A_1 - (A_1 - 150)N^c$$

$$B = (e - 1.5)N^c + 1.5$$

A represents the 37 % dose slope which varies in accordance with the formula presented above. It is assumed that the 37 % dose slope is 150 rad at the first irradiation. This value holds good, at least approximately, in most cases where cells have been irradiated. During the fractionated irradiation, the value changes towards 1, which has been assumed to lie between 250 and 450 rad. Exponent c determines the speed of the change, and if this is varied it might be possible to determine the speed. B represents the extrapolation number, defined by the formula presented above. Also here, c determines the speed of the change. e is the extrapolation number at the first irradiation and changes towards 1.5. The value 1.5 was arrived at from the calculations in the next section.

The relative closeness of fit was also determined by means of formula (3).

Results and Discussion

In all the calculations, use was made of the experimental results published by FOWLER (1965), as shown in Fig. 6 and in the Table. The numerical calculations were effected with the Elliot 803 Computer at the Department of Theoretical Physics, University of Helsinki.

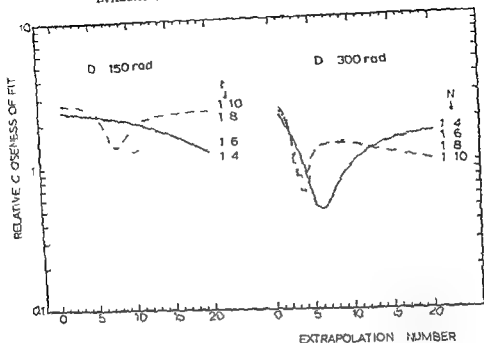


Fig. 1 Results of calculations with formulas (2) and (3). N indicates the interval of fractions included in the calculations. The curves depict results of the study of fractions from 1 to 10.

As has been demonstrated by WOORTOV (1966), the change in the total dose D for five irradiations or more, can be expressed by the formula

$$D = D_1 N \quad (6)$$

where N is the number of fractions and D the total dose needed in N fractions to arrive at the same survival proportion as for another irradiation number exceeding four. D_1 is the extrapolated iso effect dose in one fraction and a is a constant characteristic of the tissue system.

These facts led to the assumption that the theory would provide a better fit for the experimental results if account were taken only of the results between the eighth and the last irradiation. Initially, however, all the experimental results were included in the calculations but subsequently the initial and subsequent parts of the fractionation results were examined separately.

Formulas (2) and (3) were used. At first D_0 was varied from 50 to 500 rad in steps of 50 rad and m from 1 to 20 in steps of 1. When Q was near minimum it was examined more carefully by changing D_0 and m , in small steps in the

$$S_N = x\{1 - (1 - e^{-D/N D_1})^{m_1}\}^N + (1-x)\{1 - (1 - e^{-D/N D_2})^{m_2}\}^N \quad (4)$$

x is the proportion of 'radiosensitive' cells at the beginning of the irradiation. Thus, $(1-x)$ is the proportion of the 'radioresistant' cells, D the total dose, N the number of fractions and D/N the dose per fraction as defined earlier. D_1 and D_2 are the 37 % dose slopes, and m_1 and m_2 the extrapolation numbers of the 'radiosensitive' and 'radioresistant' cells, respectively.

The criterion for closeness of fit given in formula (3) was also applied in the calculation with formula (4).

Cell population with varying parameters A further model, in which parameters m and D_0 change during the fractionated treatment, was also studied. The formula corresponds to a cell population which changes to a more 'radioresistant' one with an increasing number of fractions.

$$S_N = \{1 - (1 - e^{-D/N A})^B\}^N \quad (5)$$

where

$$A = A_1 - (A_1 - 150)N^e$$

$$B = (e - 1.5)N^e + 1.5$$

A represents the 37 % dose slope which varies in accordance with the formula presented above. It is assumed that the 37 % dose slope is 150 rad at the first irradiation. This value holds good, at least approximately, in most cases where cells have been irradiated. During the fractionated irradiation, the value changes towards A_1 , which has been assumed to lie between 250 and 450 rad. Exponent e determines the speed of the change, and if this is varied it might be possible to determine the speed. B represents the extrapolation number, defined by the formula presented above. Also here e determines the speed of the change. e is the extrapolation number at the first irradiation and changes towards 1.5. The value 1.5 was arrived at from the calculations in the next section.

The relative closeness of fit was also determined by means of formula (3).

Results and Discussion

In all the calculations, use was made of the experimental results published by FOWLER (1965), as shown in Fig. 6 and in the Table. The numerical calculations were effected with the Elliot 803 Computer at the Department of Theoretical Physics, University of Helsinki.

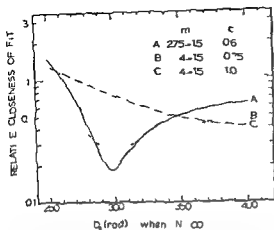


Fig 3 Results of calculations with formula (5). The minima at 300 rad show that the 37% dose slope changes from its initial value of 150 rad to about 300 rad. The values of m and c are indicated in the figure.

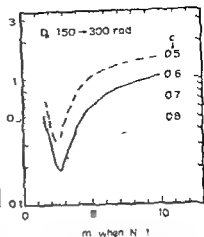


Fig 4 Calculations illustrating how the extrapolation number m changes between 2 and 4 to 1.5 when formula (5) is applied. The value of D is indicated in the figure.

m exceeds 2 at the beginning of irradiation and diminishes towards 1 during fractionation. Nothing can be said about the dose slope D_0 from the results of calculations.

If we start from the assumption that at the first irradiation $D_0 = 150$ rad, m is between 2 and 10 and the total dose is 2000 rad (FOWLER) then after this irradiation the survival proportion will be $S = 0.3 \times 1.6 \times 10^{-3}$. If it is assumed that $\lambda = 30$ i.e. 30 irradiations $m = 1.6$ and $D = 200$ rad per irradiation (FOWLER) there must be $D_0 = 280$ to 310 rad to arrive at the same survival proportion. This involves a change in D_0 from 150 to about 300 rad.

The calculations with application of formula (3) a mixture of two cell types did not provide any acceptable results. In these calculations the radiosensitive cells were assumed to have the 37% dose slope $D_1 = 150$ rad and the extrapolation number $m_1 = 2$ to 15; the radioresistant cells had $D_2 = 150$ to 450 rad and $m_2 = 1.6$ respectively. The best results were obtained for $m_1 = 5$ to 8 and $D_2 = 300$ to 400 rad, but the smallest value of Q was about 1.8. (This type of cell population does not seem useful in the application of the single hit multi-target model.)

Finally we employed formula (4) for a cell population in which the parameters change during the fractionated irradiation. The starting assumption was that D_0 is 150 rad at the first irradiation and changes towards a higher value 250 to 400 rad with an increasing number of irradiations. The values

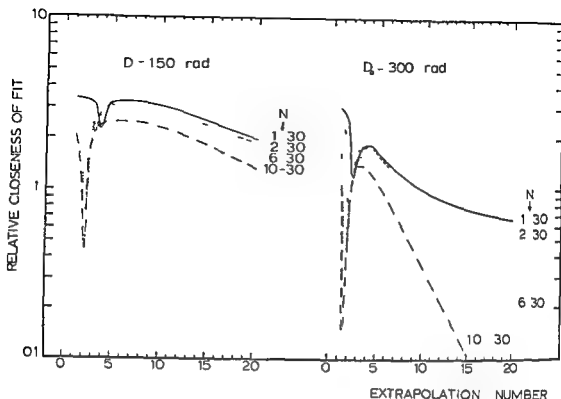


Fig 2 Results of calculations with formulas (2) and (3) on the study of fractions from 1 to 30 (Compare legend to fig 1)

region near the minimum. The experimental dose D should produce the same S_A , regardless of the number of fractions. The obtained quantity of O should accordingly at its minimum give the values of D_0 and m that best describe the experimental results. The results for $D_0=150$ rad and $D_0=300$ rad appear in Figs 1 and 2.

It may be observed that, independently of D_0 , the value of m moves towards a value of about 1.6 if the total doses D for small numbers of N are neglected. This means that during the fractionation m falls from its initial value, probably between 2 and 10, to about 1.6. This is discernible from the curves in which the calculations include N from 1 to 30 and from 10 to 30. Moreover, the curves based on N values from 1 to 10 indicate that at the beginning of the treatment m is higher than 3.5 for $D_0=150$ rad, and higher than 2 for higher D_0 values. The agreement between experiment and theory is usually better on an increase in D_0 . It has been assumed that the minima at low m values are the realistic ones until experimental evidence in support of higher extrapolation numbers may be brought forward. The final conclusion is that the extrapolation number

Table

Comparison of experimental and theoretical results

Number of fractions N	Experimental results FOWLER (1965) $D_{\text{tot } 1} \text{ (rad)}$	Theoretical results based upon the single hit multi target model				
		$D = 150 \text{ rad}$ $m = 3.5$ $S = 4.50 \times 10$ $D_{\text{total}} \text{ (rad)}$	$D = 300 \text{ rad}$ $m = 1.6$ $S = 1.12 \times 10$ $D_{\text{total}} \text{ (rad)}$	Formula (5) $c = 0.6$ $S = 5.44 \times 10$		
				$D_{\text{total}} \text{ (rad)}$	$D \text{ (rad)}$	m
30	6 000	6 240	6 000	6 030	281	1.67
20	5 460 \pm 30	5 140	5 360	5 500	275	1.71
15	5 070 \pm 70	4 500	5 025	5 100	270	1.75
12	4 810 \pm 70	4 100	4 800	4 780	266	1.78
10	4 560 \pm 70	3 800	4 620	4 500	262	1.81
8	4 300 \pm 80	3 500	4 410	4 280	257	1.87
6	4 010 \pm 80	3 170	4 220	3 940	249	1.93
4	3 490 \pm 120	2 830	3 920	3 500	235	2.04
2	2 730 \pm 160	2 475	3 690	2 780	201	2.33
1	2 000 \pm 250	2 265	3 553	1 970	150	2.75

The changes in the parameters are rather rapid and they may be considerable even after four irradiations as can be seen from the Table and Fig 5 in which the results of calculations are compared with the experimental findings of FOWLER. Close agreement may be attained if the last model proposed in the form of formula (5), is applied.

It would seem that the present findings should be taken into consideration in connection with fractionated irradiation of cell populations or in connection with fractionated radiotherapy.

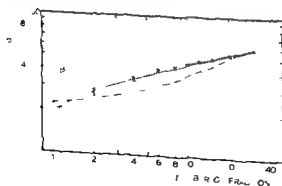


Fig 6 A comparison of experimental results (FOWLER 1965) with theoretical calculations. Curve A is derived from formula (2) with $D = 150 \text{ rad}$ and $m = 3.5$. Curve B gives similar results with $D = 300 \text{ rad}$ and $m = 1.6$. Curve C is the best fit on application of formula (5). The values of the parameters D , m and c are contained in the Table presented.

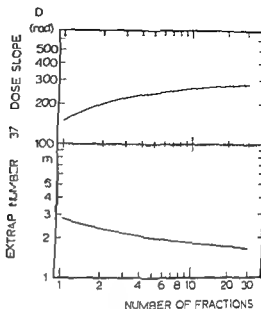


Fig 5 Curves showing the change in D_0 and m for the best fit obtained with formula (5)

used for m were from 1.5 to 15 at the first irradiation, these were allowed to change towards 1.5. The variation in both parameters was determined by the formula presented in the preceding section. The results of calculations, some of them presented in Figs 3 and 4, indicate that the best agreement between theory and experiment, i.e. the smallest values of Ω , was arrived at on a change in D_0 from 150 to 300 rad, in m from 2.75 to 1.5, and to have $c=0.6$. The value of c is sharply determined, which means that the change in D_0 and m becomes apparent. Fig 5 indicates the change in D_0 and m when $c=0.6$. The results should be so understood that for a definite number of fractions the values of D_0 and m are average values which correspond to that particular number of fractions. In fact, the value of D_0 is less than that of the average value at the beginning of the fractionated irradiation, and larger in the later part. Similarly when N irradiations are made, the value of m exceeds its average at the beginning, and is smaller at the end of the irradiations.

In conclusion, the last model seems the best one for describing the change in the total dose during fractionated irradiations of cells. It was assumed that during the irradiations the 37% dose slope changes from its initial value of 150 rad to about 300 rad. The extrapolation number has a value between 2 and 4 at the beginning, and changes towards about 1.5 at the end of the fractionated treatment.

The results now arrived at seem to confirm the view that the radioresistance of irradiated cell populations may change during fractionated treatment.

Table
Comparison of experimental and theoretical results

Number of fractions	Experimental results FOWLER (1965) D_{total} (rad)	Theoretical results based upon the single hit multi target model				
		$D = 150$ rad $m = 3.5$ $S = 4.50 \times 10$ D_{total} (rad)	$D = 300$ rad $m = 1.6$ $S = 1.12 \times 10^{-4}$ D_{total} (rad)	Formula (5) $c=0.6$ $S = 5.44 \times 10$ D_{total} (rad)	D (rad)	m
30	6000	6240	6000	6030	281	1.66
20	5460 \pm 50	5140	5360	5500	275	1.71
15	5070 \pm 70	4500	5025	5100	270	1.75
12	4810 \pm 70	4100	4800	4780	266	1.78
10	4560 \pm 70	3800	4670	4500	267	1.81
8	4300 \pm 80	3500	4410	4280	257	1.86
6	4010 \pm 80	3170	4220	3940	249	1.93
4	3490 \pm 120	2830	3920	3500	235	2.04
2	2730 \pm 160	2475	3690	2780	201	2.33
1	2000 \pm 250	2265	3355	1970	150	2.75

The changes in the parameters are rather rapid and they may be considerable even after four irradiations as can be seen from the Table and Fig 6, in which the results of calculations are compared with the experimental findings of FOWLER. Close agreement may be attained if the last model, proposed in the form of formula (5) is applied.

It would seem that the present findings should be taken into consideration in connection with fractionated irradiation of cell populations or in connection with fractionated radiotherapy.

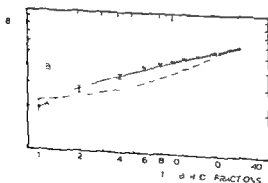


Fig 3 A comparison of experimental results (FOWLER 1965) with theoretical calculations. Curve A is derived from formula (2) with $D = 150$ rad and $m = 3.5$. Curve B gives similar results with $D = 300$ rad and $m = 1.6$. Curve C is the best fit on application of formula (5). The values of the parameters D , m and c are contained in the Table presented.

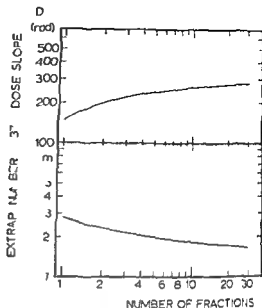


Fig. 5. Curves showing the change in D_0 and m for the best fit obtained with formula (5).

used for m were from 1.5 to 15 at the first irradiation, these were allowed to change towards 1.5. The variation in both parameters was determined by the formula presented in the preceding section. The results of calculations, some of them presented in Figs 3 and 4, indicate that the best agreement between theory and experiment, i.e. the smallest values of Q , was arrived at on a change in D_0 from 150 to 300 rad, in m from 2.75 to 1.5, and to have $c=0.6$. The value of c is sharply determined, which means that the change in D_0 and m becomes apparent. Fig. 5 indicates the change in D_0 and m when $c=0.6$. The results should be so understood that for a definite number of fractions the values of D_0 and m are average values which correspond to that particular number of fractions. In fact, the value of D_0 is less than that of the average value at the beginning of the fractionated irradiation, and larger in the later part. Similarly when N irradiations are made, the value of m exceeds its average at the beginning, and is smaller at the end of the irradiations.

In conclusion, the last model seems the best one for describing the change in the total dose during fractionated irradiations of cells. It was assumed that during the irradiations the 37% dose slope changes from its initial value of 150 rad to about 300 rad. The extrapolation number has a value between 2 and 4 at the beginning, and changes towards about 1.5 at the end of the fractionated treatment.

The results now arrived at seem to confirm the view that the radioresistance of irradiated cell populations may change during fractionated treatment.

LATE RESULTS FOLLOWING RADIOTHERAPY OF SKIN CANCER

by

P. BJERRE HANSEN and M. SCHARLING JENSEN

Radiotherapy of carcinoma of the skin was first tried in 1899 and has for the last half century been acknowledged as an effective and comparatively non-injurious method of treatment. The application of radium was the method of choice in the first decades but¹ during the last twenty years or so low voltage roentgen therapy has predominated.

The literature regarding radiotherapy of carcinoma of the skin is extensive and includes so many comprehensive Scandinavian contributions that an adequate impression of the development in this field may be obtained by reference to the publications of NORDENTORF (1914) COLLIN (1928) NIELSEN (1933 1951) MACNELSON (1935) EBBENOJ (1936—1951) HULTBERG (1943) MOSE WILDE (1951) SCHMIDT & AMORLP (1953) KLORNING (1959) JOHANSEN (1961) and JENSEN (1965). Radium treatment was the main theme of the earlier studies with EBBENOJ, HULTBERG and later investigators concerned themselves mainly with roentgen therapy.

The results of radiotherapy of carcinoma of the skin are in the majority of studies assessed as survival rates after 5 years observation. This survival criterion

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SUMMARY

The experimental results of FOWLER (1965) of the change in the total dose with an increasing number of irradiations of cells have been compared with theoretical calculations based upon the single hit, multi target model

ZUSAMMENFASSUNG

Die experimentellen Untersuchungen von FOWLER (1965) über die Veränderung der Totaldosis mit zunehmender Anzahl fraktionierter Bestrahlungen von Zellen wurden mit theoretischen Berechnungen verglichen die auf Basis der Treffertheorie mit einem single hit multi target Modell durchgeführt wurden

RÉSUMÉ

Les résultats expérimentaux de FOWLER (1965) sur la modification de la dose totale quand on augmente le nombre des irradiations des cellules ont été comparés avec les calculs théoriques basés sur le modèle du coup unique à cible multiple

REFERENCES

- DIENES G J. A kinetic model of biological radiation response *Radiat Res* 28 (1966) 183
- FOWLER J F. The estimation of total dose for different numbers of fractions in radiotherapy *Brit J Radiol* 38 (1965) 365
- and STERN B E. Fractionation and dose rate. II Dose time relationships in radiotherapy and the validity of cell survival curve models *Brit J Radiol* 36 (1963) 163
- FORSYELL G. Experiences in the permanency of radiological cure in cancer *Amer J Roentgenol* 12 (1924) 301
- HIGGINS G K. The radiosensitivity of tumors. In *Treatment of cancer and allied diseases* I. Edited by G T Pack and I M Ariele. Paul B Hoeber Inc. New York 1958
- OLIVER R and SHEPSTONE B J. Some practical considerations in determining the parameters for multi target and multi hit survival curves *Phys Med Biol* 9 (1964) 167
- WARREN S. Neoplasms. In *Pathology*. Edited by W A D Anderson. C V Mosby. St Louis 1957
- WOOTTON P. Treatment fractionation in new radiation therapy modalities *Amer J Roentgenol* 96 (1966) 871
- ZIMMER K G. *Quantitative radiation biology*. Oliver & Boyd Ltd. Edinburgh 1961

Table 1 (cont.)

Radium puncture			
<100	100-300	>300	Total
23	28	13	64
31	25	11	67
8	3	2	13
79.5	89.3	84.6	83.7
25	17	9	51
20	15	8	43
5	2	1	8
80	(88.2)	(88.9)	84.3

flat boxes or moulages, or inserted in needle shaped radium containers at intervals of 5 mm into the tumour tissue respectively. The radiation dose has been expressed as the product of the amount of radium used in milligrams and the treatment time in hours i.e. mgh.

The dose was between 700 and 1 200 mgh in almost 150 cases of contact therapy. This corresponds to a dose of between 100 and 150 mgh/cm² to the field of treatment i.e. the tumour surface which has rarely measured more than 5 to 6 cm plus a safety margin of about 1 cm and to an approximated tumour dose of around 1 800 R at a depth of 5 mm. The dose in 21 cases has been lower than 500 mgh corresponding to approximately 50 to 80 mgh/cm² and a tumour dose around 1 000 R at a depth of 5 mm.

The radium contact treatment has resulted in freedom from recurrence in 71.5% of all cases and in 73.8% of the 107 cases observed for at least 10 years (Table 1). The frequency of recurrence in relation to the doses applied has been approximately 25% after doses of around 700 to 800 mgh whilst recurrence has occurred in ten of the 21 cases in group I where the dose has been lower than 500 mgh. These results are rather poor doubtless due to underdosage particularly in group I.

The radium puncture treatment has been performed with from 2 to 7 needles loaded with 5 or 10 mg of radium and the period of treatment has most frequently been 4 to 5 hours. The dose expressed in milligram hours has varied from 40 to 500 but has generally been between 80 and 200 mgh.

Table 1 reveals that recurrence developed after radium puncture in thirteen

Table 1

Relationship between results and doses in radium treatment of skin cancer

Dose in mgh	Radium contact therapy			
	<500	500—1000	>1000	Total
Number of growths treated	21	107	72	200
= recurrences	11	80	2	143
+ recurrences	10	27	20	57
Freedom from recurrence %	52.4	74.8	72.3	71.5
Number of growths observed after treatment	11	63	31	107
= recurrences	6	49	24	79
+ recurrences	5	16	7	28
Freedom from recurrence	(54.5)	73.4	77.5	73.8

plays, however, a minor role in the evaluation of the results of treatment of skin cancer because the condition carries a very low mortality. This means that relatively large numbers of these carcinomas may be observed for as long periods as ten years or more after treatment.

Surveys with regard to the late results of radiotherapy of skin cancer, and of the cosmetic and functional results, are not very common (see, however, KJØRNING 1959, and JENSEN 1965).

A total of 1827 cases of skin cancer, referred for treatment to the Odense Radium Centre during the period 1937—1955 have been reviewed in an attempt to throw some light on these problems. A follow up study of the surviving 298 patients was carried out during 1965. A detailed survey of these studies was given to the University of Copenhagen in a special report (JENSEN). The various methods of irradiation used are now discussed in more detail in relation to the results obtained. The material has for this purpose been limited to 1198 lesions definitely verified histologically as superficial epithelial carcinomas and primarily subjected to radiotherapy. It should be noted that epithelial carcinomas, localized to the lips and to the female and male genital regions, are not included since these differ clinically and therapeutically from other skin carcinomas.

Radium treatment of skin carcinoma Radium treatment was frequently used until about 1943 but since then only occasionally. The treatment was given as 'contact therapy' in 200 cases and as 'radium puncture' in 80 cases. This means application of radium sources on the surface of the tumour, either packed in

Table 2 (cont.)

Treatment with 60 kV

I	I	2-4	5-7	8-15	Total
3 000	3 000-5 000	1 000-3 000	500-1 000	300-500	
3 000	4 000	5 000	3 500-5 000	4 000-4 500	
2 000	2 600	3 300	2 800	2 700	
213	138	103	148	83	685
III	120	93	122	50	567
31	18	10	26	33	118
85.4	87	90.3	87.5	60.3	87.8
83	58	38	72	53	304
70	52	35	57	29	243
13	6	3	15	24	61
84.2	89.6	97	79.2	54.7	79.9
125	83	58	73	24	363
103	71	50	57	17	298
22	12	8	16	7	65
82.4	85.6	86.7	78.4	70.8	82.1

Finally it should be mentioned that other methods of radium treatment and combined roentgen and radium therapy have been used primarily in a further 32 cases. This group is not registered in the tables.

Roentgen therapy of skin cancer Roentgen therapy has been given throughout the 19 year period as soft radiation with a beam quality corresponding to half value layers (HVL) in skin from 6 to 10 mm (685 cases) or since 1950 with ultra soft roentgen rays with a HVL in skin of approximately 2 mm (163 cases). The two types of roentgen radiation correspond with regard to voltage, filament current, filtration and focus-skin distance to 60 kV, 15 mA, 0.4 to 0.5 mm Al and 3 to 7 cm and 30 kV, 15 mA, 0.2 mm Al and 10 cm respectively. They will in the following be referred to as 60 kV and 30 kV. Both have been given either as a single (one sitting) treatment with doses in air of from 3 000 to

Table 2¹*Relationship between results and doses in roentgen treatment of skin cancer*

Treatment with 30 kV					
	1	1	2-4	4-7	Total
Number of treatments	1	1	2-4	4-7	
Single dose (R in air)	3 000	3 000-5 000	1 000-3 000	500-1 000	
Mean total dose (R in air)	2 800-3 000	4 200	3 000-4 000	3 500-4 500	
Mean tumor dose ¹	1 800-2 000	2 800	2 400	2 600	
Number of growths treated	33	57	50	23	163
= Recurrences	23	52	40	20	135
+ Recurrences	10	5	10	3	28
Freedom from recurrence	70	91.2 %	80	87 %	82.8 %
Number of spinocellular and mixed carcinomas	10	13	13	6	42
= Recurrences	7	11	9	5	32
+ Recurrences	3	2	4	1	10
Freedom from recurrence	7/10	11/13	9/13	5/6	76.2 %
Number of growths observed					
> 10 years after treatment	33	33	34	13	93
= Recurrences	11	31	26	11	79
+ Recurrences	5	2	8	2	17
Freedom from recurrence	8/13	91 %	76.5	11/13	81.7

¹ At 1.5 mm depth for 30 kV and 5 mm depth for 60 kV

of the 80 cases and in eight of the 51 cases observed for 10 years or more. This gives a cure rate of approximately 84 % in both groups. The results following radium puncture are thus somewhat better than those after contact treatment. This difference is statistically significant, as p is less than 0.05.

A calculation of the exact tumour dose in the various cases is not possible because information regarding the true dimensions of the tumours and the detailed positioning of the radium needles is inadequate. An average estimation suggests however that the tumour dose in the majority of cases has been of the order of magnitude around 2 500 R at a distance of 5 mm from the radium sources.

Contact therapy, because of the poor results, has been practically abandoned for treatment of skin cancer. Radium puncture is almost exclusively limited to the treatment of lip cancer and urethral orifice carcinoma. These are however as previously mentioned, not included in the present survey.

Table 2 (cont.)

Treatment with 60 kV

	1	2-4	5-7	8-15	Total
3 000	3 000-5 000	1 000-3 000	500-1 000	300-500	
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2 000	2 600	3 300	2 800	2 100	
213	138	105	148	111	685
187	120	93	122	50	567
81	18	10	26	33	118
85.4	87	90.3	82.5	60.3	82.8
83	58	58	72	53	304
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Number of growths observed					
> 10 years after treatment	13	34	34	13	93
= Recurrences	8	31	26	11	76
+ Recurrences	5	2	8	2	17
Freedom from recurrence	8/13	91°	76.5	11/13	81.7

¹ At 1 mm depth for 30 kV and 5 mm depth for 60 kV

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13	6	3	15	24	61
84.2	89.6	97	79.2	54.7	199
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4 200 R, or as a fractionated treatment, consisting mainly in a course of 2 to 4 or 5 to 7 treatments in as many days, with daily doses of approximately 1 000 or 600 to 800 R, respectively (see Table 2)

The tumour doses cannot be calculated exactly because precise information regarding the dimensions of the mass and the size of the field in the vast majority of the cases is uncertain or lacking. However, an attempt has been made to estimate the average magnitude of the tumour dose for each of the different groups treated (Table 2). It must be emphasized in this connection that a prerequisite for the use of 30 kV treatment is that the tumour tissue can be removed by scraping so that treatment field is flat and level, in order to ensure a uniform dose distribution, which is essential for the effectiveness of these soft roentgen rays. Therapy at 30 kV can therefore be used only for the treatment of superficial tumours localized to smooth skin surfaces, and with a maximal diameter of 15 to 18 mm. This means that the field of irradiation after scraping must not exceed 6 to 7 cm, including a safety zone of at least 5 mm around the tumour site.

Therapy at 30 kV has been given as a one sitting treatment in 90 cases. The dose in air has been between 2 500 and 3 000 R in 33 cases and approximately 4 200 R in 57 cases. The results were considerably poorer in the first than in the second group as the recurrence rates were 30 % and 8.8 % respectively. This difference is statistically significant ($0.001 < p < 0.01$). This was recognized in 1952, and the dose in air was accordingly increased to 4 200 R (corresponding to a tumour dose of approximately 2 800 R). This resulted in an improved cure rate around 93 %. Incidentally the dose was later (1958) increased to 5 000 R (corresponding to a tumour dose of about 3 400 R). The majority of small skin carcinomas are still treated in this manner when the above mentioned requirements as to size and flatness of the field of treatment are complied with. They are cured in about 95 % of cases.

Therapy at 60 kV has been given as a one sitting treatment in 351 cases throughout the whole period, and has mainly been used for the treatment of growths with diameters up to between 20 and 25 mm and a thickness of up to between 5 and 6 mm. The tumour dose has been approximately 2 000 R in 213 cases and about 2 600 R in 138 cases treated after 1952. The frequency of recurrence in the two groups has been 14.6 % and 13 % respectively, and for the cases observed for 10 years or longer it has been 17.6 % and 14.5 %.

A cure rate of approximately 85 % is, however, a somewhat poor outcome compared with the results obtained after 30 kV therapy given at one sitting with a tumour dose of approximately 2 800 R which in addition produces better cosmetic results. Accordingly, the one sitting treatment with 60 kV has been abandoned.

Fractionated irradiation has been used simultaneously with the one sitting treatment throughout the period as 60 kV treatment in 334 cases and as 30 kV treatment (1950—1953) in 73 cases. The fractionation and doses are registered in Table 2. The most frequent procedure has been three to four, or five to six single treatments with doses in air of about 1 000 R or 600 to 800 R respectively given during a period of 6 to 8 days by the Strandquist scale.

Fractionated 30 kV therapy was tried in an attempt to improve the cosmetic results but without success as the frequency of recurrence in these groups was as great as 13 to 20 % due to underdosage especially in the first of these two groups.

Fractionated 60 kV treatment produced relatively good results after a tumour dose of about 3 300 R as there were only ten recurrences among the 103 cases in this group (9.7 %). The frequency of recurrence in the second group was 17.5 % presumably due to underdosage in a number of cases as the average tumour dose in this group was only about 2 800 R. In the third group there were recurrences in thirty three of 83 cases (40 %) and in seven of the 24 cases followed for 10 years or longer. This drop-out rate within the 10 years is unusually large. This as well as the bad results may certainly be explained by the fact that this group included several large tumours a number of which should have been treated either with more penetrating radiation in larger doses or by operation.

The indication for fractionated 60 kV treatment has been and is a skin carcinoma of irregular form and situated on an uneven surface with an area between 7 and 8 cm and a maximum thickness of 6 to 8 mm. The total dose at the surface should preferably be about 5 600 to 6 000 R.

A total of 848 carcinomas of the skin have been treated with soft and ultra-soft roentgen rays in the various ways mentioned. Recurrences have developed in 146 of these cases corresponding to a primary cure rate of 82.8 %. Of 456 cases observed for more than 10 years after treatment 374 remained free from recurrence corresponding to a 10-year cure rate of 82 %.

Finally roentgen therapy at 100 kV and 165—185 kV has been used as primary treatment in 34 cases of large growths. Recurrence developed in sixteen of these cases. This group is not registered in the tables.

Frequency and treatment of recurrences. Radiotherapy of the 1 198 cases of carcinoma of the skin has resulted in initial cure in a total of 955 cases. Twelve patients died because of progressive tumour growth and metastases despite treatment. In the remaining 231 cases local recurrences developed during the first year in 133 cases (57.6 %) and in 203 cases (88 %) less than 5 years after the first treatment. The longest latent period was 19 years (2 cases).

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The tumour doses cannot be calculated exactly because precise information regarding the dimensions of the mass and the size of the field in the vast majority of the cases is uncertain or lacking. However, an attempt has been made to estimate the average magnitude of the tumour dose for each of the different groups treated (Table 2). It must be emphasized in this connection that a prerequisite for the use of 30 kV treatment is that the tumour tissue can be removed by scraping so that treatment field is flat and level, in order to ensure a uniform dose distribution, which is essential for the effectiveness of these soft roentgen rays. Therapy at 30 kV can therefore be used only for the treatment of superficial tumours localized to smooth skin surfaces, and with a maximal diameter of 15 to 18 mm. This means that the field of irradiation after scraping must not exceed 6 to 7 cm², including a safety zone of at least 5 mm around the tumour site.

Therapy at 30 kV has been given as a one sitting treatment in 90 cases. The dose in air has been between 2 500 and 3 000 R in 33 cases and approximately 4 200 R in 57 cases. The results were considerably poorer in the first than in the second group as the recurrence rates were 30 % and 8.1 %, respectively. This difference is statistically significant ($0.001 < p < 0.01$). This was recognized in 1952, and the dose in air was accordingly increased to 4 200 R (corresponding to a tumour dose of approximately 2 800 R). This resulted in an improved cure rate around 93 %. Incidentally the dose was later (1958) increased to 5 000 R (corresponding to a tumour dose of about 3 400 R). The majority of small skin carcinomas are still treated in this manner when the above mentioned requirements as to size and flatness of the field of treatment, are complied with. They are cured in about 95 % of cases.

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A cure rate of approximately 80 % is, however, a somewhat poor outcome compared with the results obtained after 30 kV therapy given at one sitting with a tumour dose of approximately 2 800 R which in addition produces better cosmetic results. Accordingly, the one sitting treatment with 60 kV has been abandoned.

40 and 17 cases respectively and in a few cases this occurred up to eight times. Nineteen of these 90 patients died from progressive growth and dissemination. Seven patients died from other causes although with a verified and untreated local recurrence of the carcinoma of the skin. No further recurrences have been observed so far in the remaining 64 cases.

Lethal course and metastases Carcinoma of the skin was the cause of death of 45 patients i.e. 3.8 % of the 1198 cases treated primarily with radiotherapy. Twenty six of these died within the first 1 to 2 years after the first treatment and a further thirteen died during the following 3 year period. Of the remaining 7 patients six died between 5 and 10 years and one patient died 17 years after the initial treatment. The average age of the patients at death was 70 years and varied between 38 and 93 years. Thirty two of these 45 patients were men and fourteen women. This male predominance in mortality reflects mainly the previous observation that carcinomas of the ears are about three times as common in men than in women and have a recurrence rate of about twice the average and a mortality rate of 13.5 % compared with the average of 3.8 %.

The total number of cases of ear carcinomas was 111, eighty four of which were men and twenty seven women. The course was lethal in 15 cases (2 women and 13 men). In fourteen of these, the tumours were spinocellular or mixed carcinomas and metastases were verified in ten of these cases. The patient with a basocellular carcinoma, a man, died due to invasion of the cerebrum.

Carcinomas of the skin of the lower extremities have also presented a high mortality rate. These tumours were mainly of the spinocellular type and caused the death of three patients out of 23 (13 %). Of 85 cases of eyelid carcinomas, on the other hand, 63 of which were of the basocellular type, only three proved fatal (3.5 %). These three tumours were all spinocellular or mixed carcinomas.

This difference with regard to the lethality between ear and eyelid carcinomas which have both had recurrence rates after radiotherapy twice as great as the majority of other malignant skin conditions emphasizes the suggestion that the local effect of radiotherapy is more dependent on factors such as localization and tumour size than on the histologic type of cancers of the skin. On the other hand, however, the spinocellular and mixed carcinomas produce a far greater mortality than the basocellular carcinomas due to the fact that the spinocellular tumours produce metastases quite readily whilst the basocellular carcinomas rarely or never do so. The histologic tumour type thus bears a considerable influence on the final results of radiotherapy of carcinoma of the skin.

No cases of metastases were evident among the 700 cases of basocellular carcinomas reviewed and a lethal course was evident only in the three cases already discussed i.e. approximately 0.45 %. The remaining 43 deaths were caused by

An extraordinary recurrence rate has been found for carcinomas of the skin of the ears and eyelids, and of the lower extremities. Of all the primary tumours 9.7 %, 6.7 % and 2.1 % were situated in the ears and eyelids and in the skin of the legs, whilst approximately 15.6 %, 9.1 % and 4.1 %, respectively, of all recurrences were within these regions. The poor results of radiotherapy of carcinomas of the skin in these regions, as expressed by this high recurrence rate, are presumably due to the influence of such factors as poor vascularization and necrotic changes in the underlying cartilage or periosteum, either primarily or as a result of the radiation, through which the effect of the radiation on the tumour is diminished. Geometrical and technical difficulties, especially met with in the treatment of carcinomas of the ears, may also sometimes have caused some underdosage.

It must also be mentioned in this connection that about 75 % of the growths of ears and lower extremities have been spinocellular or mixed carcinomas, while only about 20 % have been basocellular carcinomas. This predominance of spinocellular growths, which is the reverse of the figures for the distribution of the tumour types found in all other groups of skin carcinoma in this material, was probably another factor of importance for the high recurrence rate in these two groups. In the third group with a high recurrence rate, i.e. the growths of the eyelids, the basocellular carcinomas formed the dominant tumour type, however, and amounted to 70 %. This observation, together with the finding that no distinct correlation existed between the treatment results, expressed as an initial freedom from recurrence, and the histologic types of tumour in the various groups, gives the impression that the local effect of radiotherapy is relatively independent of the histologic type of the tumour.

These considerations lead to the conclusion, as emphasized by NIELSEN (1951), that carcinoma of the skin localized to these three regions, apart from very small lesions, should primarily be treated operatively. This also applies to recurrent tumours in these regions. During the last decade, repeat radiotherapy of skin carcinomas has been almost completely abandoned in favour of plastic surgery.

The treatment of the 231 recurrent tumours in 197 cases of the present material, however, consisted in repeat roentgen therapy which was mainly given as fractionated 60 kV treatment. Freedom of recurrence was obtained in only 102 of the cases (51.7 %). Surgical treatment resulted in an initial cure in twenty one of 26 cases, and electrocoagulation or local application of podophyllin was used with success in five of 11 cases. Fifteen of these patients died from extension of growth and metastases following the first recurrence.

In about two thirds of the remaining 90 cases the second relapse occurred less than one year after treatment of the recurrence. After further treatment, which in most cases was roentgen therapy, a third and a fourth recurrence developed in

The subjective complaints and functional disorders consisted in 15 cases of itching in the scar (in some cases only after exposure to sunlight) and epiphora in 4 cases of carcinoma of the eyelid. A reduction in sight occurred after treatment of the skin of the eyelid in 3 cases but this was marked only in a case treated with radium puncture in 1939.

Of the 59 cases of recurrence, thirty six were cured after repeat roentgen treatment although in twenty two of these with comparatively poor cosmetic results. Of the remaining twenty three cases surgical treatment gave acceptable cosmetic results in nineteen cases.

Five of these patients complained of itching in the scar and two of epiphora. One patient suffered from functional disturbances following a lower leg amputation and a younger woman developed an inferiority complex after an operative procedure resulting in some deformity of the nose. The cosmetic results thus appear to be better after operative treatment than after repeat radiotherapy of recurrent carcinoma. The groups are too small to permit of a definite evaluation but the results after the extended use of plastic surgery in later years have strongly confirmed this opinion. On the whole, the cosmetic and functional side effects after irradiation of carcinoma of the skin have been comparatively slight and it is striking that so few of the patients have had any complaints.

Conclusion

The methods and results of radiotherapy of a total of 1 198 cases of carcinoma of the skin treated in the period 1937—1955 have been surveyed and compared.

Primary freedom from recurrence was obtained in 79.7 % of all the cases and in 83.6 % of the 647 cases observed for at least 10 years. Recurrences developed after the first treatment in 243 cases but approximately 80 % of these were cured after repeat radiotherapy or other mainly surgical treatment. The lethality of carcinoma of the skin in the 1 198 cases has thus been 3.8 %.

The various methods of radiotherapy have given poor immediate results in several groups mainly because of underdosage. Radium contact therapy has as a whole been insufficient as freedom from recurrence was recorded in only 7.1 % of these cases. Radium puncture and fractionated 60 kV roentgen therapy in the groups with adequate dosage resulted in initial cure in close to 90 % of the cases. The best results were obtained with 30 kV roentgen therapy in a single treatment with a dose of 4 200 R (in air). This procedure secured an initial cure of about 93 % of the tumours treated i.e. small superficial tumours.

These results on the whole are slightly inferior to or on a par with other published results.

JOHANSEN reported a five year cure rate as high as 96 % after fractionated

Table 3
Cosmetic results after radiation treatment of skin cancer

Follow up examination of 298 cases	Appearance of scars			Disfiguring
	Total	Good	Fairly good	
Cases free from recurrence after first treatment	239	186 (77.8 %)	46 (19.2 %)	7 (3.0 %)
First treatment				
30 kV 4 200 R \times 1	24	21	3	0
First treatment				
60 kV 3 000—5 000 R \times 1	61	43	14	4
Cases free from recurrence after treatment of relapse	59	26 (44.1 %)	19 (32.2 %)	14 (23.7 %)
Radiotherapy of relapse	36	14	12	10
Surgical treatment of relapse	21	12	7	2

carcinomas of the spinocellular or mixed type, with verified metastases in twenty cases. As the material included almost 450 of these, the lethality was approximately 9.5 %.

Cosmetic and functional results The cosmetic and functional results following radiation of carcinoma of the skin were evaluated in 1965 by a follow up examination of 298 cases of primarily irradiated skin cancers. Of these, 239 were cured by the initial treatment and the remaining 59 cases after repeat irradiation or other treatment.

The results of the evaluation are evident from Table 3 in which the appearances of the scars have been classified as good, fairly good or disfiguring. The objective changes that were considered were (1) depigmentation of the treated areas, (2) hyperpigmentation of the border zone, (3) atrophy of the epidermis and slight shrinking, (4) atrophy of the subcutis and loss of substance, (5) alopecia in regions covered with hair, (6) peeling or crust formation, and (7) occurrence of telangiectases in and around the scar. This scar was almost invisible in 41 of the 239 cases. In 145 cases there was moderate depigmentation and slight epidermal atrophy only. Marked depigmentation and hyperpigmentation together with moderate shrinking and telangiectases occurred in 46 cases. Loss of substance and considerable shrinking, crust formation, and marked telangiectases, in varying combinations causing an unattractive and disfiguring scar had arisen in only 7 cases.

RÉSUMÉ

Les auteurs étudient différentes méthodes de traitement par le radium et par les rayons de roentgen dans 198 cas de cancers cutanés vérifiés histologiquement au cours de la période 1937—1955. Ils examinent en détail les résultats en particulier en ce qui concerne la guérison et les séquelles cosmétiques et fonctionnelles.

REFERENCES

- COLLIN E. Om strålebehandling af nogle hyppige benigne og maligne tumorer (Danish) Ugeskr Læg 90 (1928) 1
- EJSEHOJ E. Om radiologisk behandling af cancer palpebrae Hospitalstidende 79 (1936) 717
- Experiences in the treatment of skin cancer with ultrasoft roentgen rays 1933—1936 Acta radiol 36 (1951) 17
- HULTBERG S. Untersuchungen über die Röntgennabstrahlung Acta radiol (1943) Suppl No 54
- JENSEN M. SCHARLING Københavns Universitets guldmedailleopgave Medicin D København 1965
- JOHANSEN H. Cancer cutis (In Danish) Ugeskr Læger 123 (1961) 1526
- JORGENSEN B. Preliminary experiences with podophyllin in the treatment of skin carcinoma Acta radiol 37 (1952) 150
- KJØRNING S. A. Late results of radiotherapy in cancer of the skin Acta dermatol venerol 39 (1959) 477
- MACDONALD A. H. W. Skin cancer Acta radiol (1935) Suppl No 22
- MOSEKILDE E. Result of treatment of skin cancer with ultrasoft roentgen rays in a single dose Acta radiol 36 (1951) 28
- NATIONAL CANCER INSTITUTE Monograph No 10 (1963)
- NIELSEN J. Cancer cutis (In Danish) Ugeskr Læg 95 (1933) 464
- Fra Radiumstationens Arbejdsmark (Danish) Ugeskr Læg 113 (1951) 1638
- NORDENTLOFT J. Om røntgenbehandling af hudkræft (In Danish) Ugeskr Læg 76 (1914) 1511
- SCHMIDT C. T. og ANDRUP E. Om behandling af overfladisk cancer med ultrabløde røntgenstråler (In Danish) Ugeskr Læg 115 (1953) 1590

roentgen treatment of 334 skin carcinomas EBBLHØJ obtained freedom from recurrence in 96.2 % of 174 selected cases of small carcinomas with ultra soft roentgen irradiation (12 kV and 26 kV). MOSFALDE similarly reported a cure rate of 90.4 % after treatment of 603 skin carcinomas with ultra soft roentgen therapy (one sitting, 26 kV). Freedom from recurrence occurred in 307 out of about 340 treated by HULTBERG with 30 kV and 60 kV therapy. The results of radium therapy reported by COLLIN and by NIELSEN are on a par with the findings in this material, i.e. a relative cure rate of between 70 and 75 %.

It has been demonstrated that radiotherapy to skin carcinoma must be given in doses of at least 4200 R (in air) as a one sitting treatment with 30 kV to small growths, and with a total dose of about 5600 R (in air) when fractionated 60 kV therapy is used in the treatment of larger skin tumours.

Carcinomas of the skin of the ears, eyelids and lower extremities have twice as high a recurrence rate as in other sites. This seems to be due mainly to complicating factors of anatomical and technical origin. Furthermore, the growths in the ears and the lower extremities which in 75 to 80 % of cases have been carcinomas of the spinocellular or mixed type, have possessed a high tendency to produce metastases and accordingly have had a high mortality rate, 9.5 % against the average 3.8 %.

These findings lead to the conclusion that the preferable treatment of skin carcinomas of the ear, lower extremities and maybe the eyelids (excepting very small tumours), appears to be plastic surgery rather than radiotherapy. This also applies to the majority of all recurrent skin carcinomas after initial radiotherapy, since the survival rate and the cosmetic results after repeat radiotherapy is poorer than after surgery.

The cosmetic results after one course of radiation treatment of carcinomas of the skin have on the whole been quite satisfactory. Inasmuch as disfiguring scars, itching, tenderness and malfunction have been observed only in a small percentage of cases.

SUMMARY

Various methods of radium treatment and roentgen therapy in 1198 cases of histologically verified carcinomas of the skin during the period 1937—1955 are discussed. The results particularly as regards the cure rate and cosmetic and functional sequelae are considered in detail.

ZUSAMMENFASSUNG

Ein Material von 1198 Fällen von Hautkarzinom, die mit verschiedenen Methoden von Röntgenbestrahlung und Radiumtherapie behandelt wurden, wird kritisch besprochen. Die Resultate wurden nicht nur mit Hinsicht auf Behandlungserfolge sondern auch auf die kosmetischen und funktionellen Erfolge eingehend ausgewertet.

EFFECTS OF SMALL DOSES OF RADIOACTIVE STRONTIUM ON THE RAT BONE MARROW

by

T STOKKE P OFTEDAL and A PAPPAS

Exposure of bone marrow to ionizing radiation will reduce its number of haematopoietic cells. The cell reduction and subsequent regeneration following external irradiation has been studied experimentally as well as clinically. The effect of irradiation from internal sources is to a great extent similar to that of protracted external total body irradiation with the same dosage (ALEKSANDROVA & SELIVANOVA 1963) and will be determined by several factors, such as the metabolic features of the radionuclide, the quality of the radiation and the total radiation dose.

In most of the experimental work recorded in the literature, relatively large doses of radioactive substances were administered, and the reaction of the bone marrow could easily be observed in histologic sections. The effects of small doses are more difficult to demonstrate, and our present knowledge on this subject is rather scanty.

The cell number of rat bone marrow was reduced for about 3 months following single injections of ^{90}Sr in amounts of 0.1 $\mu\text{Ci/g}$. As the radiation dose rate

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STRAHLENSCHUTZ IN FORSCHUNG UND PRAXIS Band 7 Jahrbuch der Vereinigung deutscher Strahlenschutzärzte Herausgegeben von H R Beck, W Frik H Keim und H Braun 343 Seiten 4 farbige Abbildungen 32 Abbildungen 129 Zeichnungen 29 Tabelle Rom bach, Freiburg i Br 1967 Preis 78 DM

This is a collection of lectures given during a course at Freiburg West Germany in October 1966. Most of the papers are centered on three main themes: the first being the protection of the patient as well as the personnel and third parties against unnecessary radiation in diagnostic roentgenology. Various factors of importance for the doses actually received are discussed: e.g. voltage and filtration, photographic technique, properties of films, fluoroscopy and intensifying screens, image intensifiers, TV camera tubes. It is known from practical experience that only after years of efficient training under competent guidance is the radiologist able to perform examinations with minimal dosage and optimal diagnostic value so that unnecessary retakes are avoided. This should be a warning to those with insufficient training not to overtax their capacity. Dose measurement apparatus and radiation protection materials are also discussed under this heading.

The second group of papers treats selected problems of radiobiology (the yield of free radicals by irradiation for various molecular configurations, amino acid metabolism after sublethal and lethal irradiation of mice and other animals, as well as in radiotherapy patients and the combined effects of irradiation and skin wounds on serum albumins and globulins). Histopathologic observations on radiation injuries in duodenal epithelium and other tissues and the effect of whole body irradiation on adrenal cortex activity are also included.

The third theme is medical supervision of occupationally exposed staff. The medical criteria for allowing or prohibiting a certain person to take work entailing radiation hazards are discussed in a useful way, and it is pointed out that in many borderline cases permission should be given subject to certain limitations: e.g. work with unsealed radionuclides for bidden or work permitted only with activities under a specified limit. The psychological constitution of the persons examined should be better considered than is often the rule. Three of the papers deal specifically with medical supervision at a university, a nuclear research centre and in the uranium industry as well as in the manufacture of fuel elements.

A few papers appear under the heading for discussion. They concern two different hematologic effects of radiation: a case of heavy irradiation in a criticality accident and a number of cases of skin carcinoma produced by the long carrying of quacksalver radium compresses. A warning is issued against such devices and similar uses of radium and radon.

The book will be valuable to those with various interests in radiation protection, especially diagnostic radiologists and those responsible for the medical supervision of radiologic work.

Sten Benner

Table 2

Calculated doses to bone marrow of rat femora and tibiae after injection of ^{90}Sr — ^{90}Y depression of cellularity and efficiency of radiation

Mean injected dose $\mu\text{Ci/kg}$	Observation time weeks	Dose in mrad			Percentage mean cellular depression	Efficiency per cent depression total rad
		First week	Remaining period	Total		
2.70	6	330	1010	1600	24.8	0.015
2.4	12	500	2060	2560	27.4	0.011
1.40	6	280	550	830	22.2	0.077
1.26	12	250	1020	1270	27.3	0.072
0.124	6	24	49	73	12.8	0.18
0.130	12	26	105	131	17.0	0.13
1.36 10^{-4}	6	3.5	8.1	11.6	15.9	1.4
1.42 10^{-4}	12	3.2	15.2	18.4	9.7	0.53
1.51 10^{-4}	6	0.34	0.79	1.13	0.2	0.18
1.44 10^{-4}	6	0.32	0.75	1.07	-1.0	-1.0
1.44 10^{-4}	6	0.32	0.75	1.07	3.3	3.1
1.29 10^{-4}	12	0.29	1.38	1.67	4.3	2.5
1.35 10^{-4}	12	0.30	1.45	1.75	6.6	3.8
0.95 10^{-4}	12	0.21	1.07	1.23	-0.1	-0.1
1.61 10^{-4}	18	0.36	2.66	3.02	2.3	0.76
1.26 10^{-4}	18	0.28	2.08	2.36	0.8	0.33
1.36 10^{-4}	6	0.031	0.071	0.10	2.5	2.5
1.44 10^{-4}	12	0.032	0.154	0.19	-1.6	-1.0
1.32 10^{-4}	18	0.030	0.218	0.25	2.5	1.0

rat population in the animal house of the Norwegian Radium Hospital the coefficient of variation being about 10 per cent. The variation between litter mates was considerably smaller however. In a series of 15 pairs of litter mates the variation within sibships was a third of that between sibships.

Material and Methods For the present investigation, pairs of litter mates of the same sex were used, one as test animal, the other as control. The animals were about 2 to 3 months old when injected and weighed from 135 g to 300 g. Weight difference within pairs was in general less than 20 g. Radioactive strontium chloride was injected intraperitoneally in a single dose of 0.5 or 0.25 ml made up by dilution of a stock solution. The control animal was given placebo injection of distilled water. The test animal and its control lived under identical conditions.

The animals were killed by dislocation of the neck at the end of the experi-

Table 1

Cellularity and radioactivity in rat femora and tibiae after injection of ^{90}Sr

Dose injected $\mu\text{Ci/kg}$	Observation time weeks	Percentage of cell content		Content of strontium 90		
		Mean	Range	Mean dpm	Range dpm	pCi/g Ca
2	6	75	69—81			
	12	73	67—78			
1	6	78	68—86	29 000	26 000—33 000	37 100
	12	73	68—79			
0.1	6	87	84—91	4 180	3 400—4 900	5 430
	12	83	78—88	2 660	2 570—2 800	3 460
0.01	6	81	81—88	347	269—420	450
	12	90	87—92	289	140—427	380
0.001	6	100	99—101	45	35—50	59
	6	101	97—106	47	36—66	61
	6	97	90—100	57	48—72	74
	12	96	94—98	30	8—42	39
	12	93	86—101	42	34—47	55
	12	100	99—101	29	28—30	38
	18	98	92—107	17	5—33	22
	18	99	96—103	52		68
	6	98	88—101	8		10
	12	102	99—105	6		8
0.0001	18	98	94—104	11		14

There were four and three rats in the 5th and 6th groups in the others five. In the last four groups bones were pooled within groups and no range can be given for these. Open spaces in the columns recording the ^{90}Sr content indicate that no measurement was made.

decreased during the ensuing time, restoratory processes took place, leading to a certain hyperplasia of marrow cells (VLASOV 1964).

The aim of the present investigation was to determine the dose effect relationship of small amounts of ^{90}Sr in causing detectable reduction in the number of haematopoietic cells in the bone marrow of rats. Reductions of the order of 10 to 15 per cent or more can be detected in histologic sections but cannot be expressed quantitatively in precise terms. Counting of cells in sections is difficult to perform, and the sources of error are considerable, but by using a counting chamber a high degree of accuracy may be reached and by this method numerical reductions under 10 per cent can be detected and quantitatively determined (STOKKE 1966).

The number of nucleated cells in the bone marrow will normally vary from one animal to another. This variation has previously been determined in the

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1.51 10^{-1}	6	0.34	0.79	1.13	0.2	0.18
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	6	97	90—100	57	48—72	74
	12	96	94—98	30	8—42	39
	12	93	86—101	42	34—47	55
	12	100	99—101	29	28—30	30
	18	98	92—107	17	5—33	22
	18	99	96—103	52		68
	6	98	88—101	8		10
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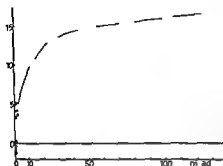


Fig 2 Percentage depression of bone marrow cellularity in relation to doses calculated to have been absorbed in marrow of femur and tibia after intraperitoneal injection of Sr the ordinate giving the mean depression of cellularity in groups of 5 test animals relative to paired $s b$ controls and the abscissa the total dose in the experimental period ○ corresponds to 6 weeks and + to 12 weeks

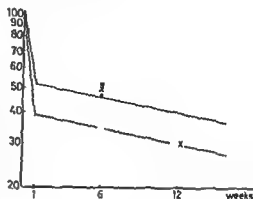
values have been used in the dose calculations. Since five animals at the most were used in each group, no attempt has been made to calculate the error of the mean, instead the range of observed values has been indicated wherever possible. The experiments were performed over a period of about two years, more or less in the order of decreasing concentrations.

Dose calculations. The results of dose calculations are given in Table 2. Retention of the intraperitoneally injected $^{86}Sr-^{86}Y$ solution has been assumed to follow a pattern similar to that after injections of ^{86}Sr in mice described by NILSSON *et coll* (1967) and in rats described by COHEN & GUSMANO (1967). These authors found by whole body counting that retention had two clearly different phases. The first phase lasted for about a week, and was characterized by a rapid excretion of about 60 per cent of the amount injected. The second phase consisted of a much slower rate of excretion.

In the present calculations the first phase has been presumed to last for a week. The rates of the two phases were determined from the skeletal content of ^{86}Sr at 6 and 12 weeks after injection (Fig 1). It was assumed that during the first week the material injected is homogeneously distributed in the whole rat and that excretion takes place at a uniform rate from all tissues. The dose absorbed by the marrow of the femora and tibiae will be determined by the mean radionuclide concentration and by the geometry of the tissues surrounding these bones (PARMELEY *et coll* 1962; BOND & FEINENDEGEN 1966).

For the remaining part of the observation period it has been assumed that $^{86}Sr-^{86}Y$ is found only in the skeleton and that the excretion takes place at a lower rate (Fig 1). This rate was taken to be independent of the amount injected, but in accordance with the observed levels of incorporation it was assumed that for the two larger injection amounts of the radionuclide about 40 per cent of the total is bound to the skeleton and for the three smaller in

Fig. 1 Presumed retention pattern of ^{86}Sr after intraperitoneal injection expressed as percentages of amount injected (ordinate) the points representing the ^{86}Sr body burden calculated from amounts measured in femora and tibiae at times given (abscissa) Semilog scale ● $1.5 \mu\text{Ci}$ per kg bodyweight + $0.15 \mu\text{Ci}$ × $0.015 \mu\text{Ci}$ and ○ $0.0015 \mu\text{Ci}$ (approximate concentrations) It should be observed that the two symbols + and × are meant to coincide at 12 weeks and should have been superimposed but have for the sake of clarity been given separately



mental period. The marrow in the shafts of both femora and tibiae were taken out in separate aliquots, weighed, suspended in 3 per cent acetic acid, and transferred to a Burkers counting chamber for counting (Stokke 1966). The counts were recorded as the number of cells per milligram of marrow, and the mean of these four counts from the test animal was expressed as a percentage of the corresponding value from the control. Experiments were usually performed with five pairs of animals for each dose.

The length of the experimental period and the magnitude of the dose were determined in preliminary experiments. The minimum useful time of observation was found to be 6 weeks with the small doses used, after this time conditions became fairly stabilized.

The bone marrow of the femora and tibia was removed, and the ^{86}Sr content of the bony parts determined. This was done by radiochemical isolation of strontium, followed by standard and low level proportional β counting. The results have been expressed as disintegrations per minute per gram of bone ash. The determination of radioactivity in the bone ash was carried out separately for each test animal, and the group mean value calculated. Excepted were the groups injected with the smallest amounts of ^{86}Sr , in which the skeletal parts from the five test animals of the group were pooled in one analysis. The background was determined by pooling all skeletal material of the control animals of the group. This value has been subtracted from the mean and range values of the corresponding test group. The results are presented in Table 1 as $\mu\text{Ci } ^{86}\text{Sr/g Ca}$ on the basis of 35 per cent Ca in the bone ash.

Observations. The observations are summarized in Table 1. It will be noted that the amount injected was constant within each group, and the concentration will therefore vary inversely with the weight of the rat. The values in the first column therefore give only the order of magnitude of concentration. Exact

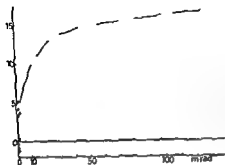


Fig. 2 Percentage depression of bone marrow cellularity in relation to doses calculated to have been absorbed in marrow of femur and tibia after intraperitoneal injection of ^{90}Sr the ordinate giving the mean depression of cellularity in groups of 5 test animals relative to paired Hb controls and the abscissa the total dose in the experimental period \bigcirc corresponds to 6 weeks and $+$ to 12 weeks

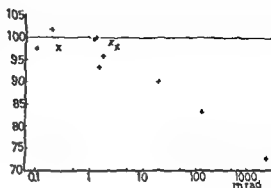
values have been used in the dose calculations. Since five animals at the most were used in each group no attempt has been made to calculate the error of the mean, instead the range of observed values has been indicated wherever possible. The experiments were performed over a period of about two years, more or less in the order of decreasing concentrations.

Dose calculations. The results of dose calculations are given in Table 2. Retention of the intraperitoneally injected ^{90}Sr solution has been assumed to follow a pattern similar to that after injections of ^{90}Sr in mice described by Nilsson *et al.* (1967) and in rats described by Corr & Gusmano (1967). These authors found by whole body counting that retention had two clearly different phases. The first phase lasted for about a week and was characterized by a rapid excretion of about 60 per cent of the amount injected. The second phase consisted of a much slower rate of excretion.

In the present calculations the first phase has been presumed to last for a week. The rates of the two phases were determined from the skeletal content of ^{90}Sr at 6 and 12 weeks after injection (Fig. 1). It was assumed that during the first week the material injected is homogeneously distributed in the whole rat and that excretion takes place at a uniform rate from all tissues. The dose absorbed by the marrow of the femora and tibiae will be determined by the mean radionuclide concentration and by the geometry of the tissues surrounding these bones (Parnley *et al.* 1962; Boyd & Fernendezen 1966).

For the remaining part of the observation period it has been assumed that ^{90}Sr is found only in the skeleton and that the excretion takes place at a lower rate (Fig. 1). This rate was taken to be independent of the amount injected, but in accordance with the observed levels of incorporation it was assumed that for the two larger injection amounts of the radionuclide about 40 per cent of the total is bound to the skeleton and for the three smaller in

Fig 3 Percentage cellularity of bone marrow in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of ^{90}Sr the ordinate giving the mean cellularity in groups of 5 test animals relative to paired sub control and the abscissa the total dose in the experimental period. Semilog scale. \circ corresponds to 6 weeks + to 12 weeks and \times to 18 weeks



jection amounts about 50 per cent. The doses absorbed by the bone marrow have been calculated on these assumptions and on the basis of the theoretical and calculated absorption constants of PARMLEY *et al.* (loc. cit.). The doses calculated for the two excretion phases, as well as the efficiency of radiation calculated in terms of percentage cellular depression in the bone marrow per rad total dose, are given in Table 2.

In Fig. 2, the cellularity of the bone marrow has been plotted against the total doses calculated in the lower range. It will be seen that the relationship between calculated doses and the depression of cellularity is not easily interpreted. It appears that doses in the ten millirad range lead to a depression by some 10 to 15 per cent, and that even a few millirad may have some effect. A biphasic reaction pattern in relation to the dose appears possible.

It appeared by plotting the data on a semilog scale as shown in Fig. 3 that the effect beyond the dose range of a few millirad may be described by a power law, the effect being proportional to the logarithm of the dose. For the two lower groups of doses the data do not conform to this description.

Finally, it was revealed by plotting the efficiency of the radiation on a log-log scale as in Fig. 4 that the radiation efficiency at all dose levels appears to be limited by the line $\log \text{efficiency} = -\text{const} \log \text{dose}$.

However, in the lowest dose range, where both positive and negative values are observed, the validity of this hyperbolic function is quite uncertain.

The present material is not large enough to determine how the cellularity varies with time within any of the dose groups. In the range of 1 to 3 mrad where there are several observations at the 6, 12 and 18 week periods, it could be surmised that a steady state situation might be present. However, the effects are not unambiguous, and no definite conclusion can be drawn.

The present material permits no differentiation between the effects of the

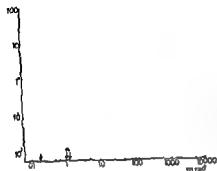


Fig. 4. Efficiency of radiation (i.e. percentage depression of bone marrow cellularity per rad) in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of ^{90}Sr the ordinate giving the depression per rad total dose over the experimental period and the abscissa the total dose in the experimental period. Log-log scale. The arrows indicate three cases of negative depression: \circ corresponds to 0 weeks, $+$ to 4 to 12 weeks and \times to 8 to 18 weeks.

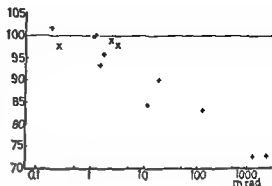
relatively high dose of the first week and those of the lower but approximately constant dose rate of the subsequent period. This is because a high or low dose during the first week is invariably associated with a similarly high or low dose during the remaining observation period. According to NILSSON (1967) the latter phase is more important for tumor induction in mice. If the cellular depression observed is in fact the reflection of a steady state situation (LAMERTON 1961, 1968), one would likewise expect the long term dose rate to be of decisive importance since recovery from the dose of the first week should be completed long before the first observation at 6 weeks.

Discussion

Whatever the biologic significance of the reduction of bone marrow cellularity it is interesting that it appears possible to demonstrate a biologic effect in mammals at a dose level of a few millirad per week. Biologic effects in the millirad range have so far been observed only in experiments on fungal growth rate (FORSBERG 1943).

The present dose calculations are not extreme in one direction or another. Due to the quantitative limits determined by the amount of radioactivity injected and by the concentration measured in the skeleton the leeway afforded for more extreme values is not great. The dose of the rapid excretion phase would certainly be higher if this phase were to last longer than observed in the mouse. However, if it were to last for two weeks instead of one, the dose contribution of this phase would increase by at most one third of that calculated at present. It appears possible, on the basis of the data of CORN & GLISMANO (1967) obtained with considerably higher amounts of radioactivity, that this phase is in fact shorter. Furthermore, it could be that the dose accumulated during the

Fig. 3 Percentage cellularity of bone marrow in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of ^{90}Sr the ordinate giving the mean cellularity in groups of 5 test animals relative to paired sub control and the abscissa the total dose in the experimental period. Semilog scale. \circ corresponds to 6 weeks + to 12 weeks and \times to 18 weeks



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However, in the lowest dose range, where both positive and negative values are observed, the validity of this hyperbolic function is quite uncertain.

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The present material permits no differentiation between the effects of the

- LUNING K G FROLÉN H NELSON A and RÖNNBACK C Genetic effects of strontium 90 injected into male mice *Nature* 197 (1963) 304
- Genetic effects of strontium 90 on immature germ cells in mice *Nature* 199 (1963) 303
- MÜLLER W A Gonad dose in male mice after incorporation of strontium 90 *Nature* 214 (1967) 931
- NILSSON A Influence of gestation and lactation on radiostrontium induced malignancies in mice *Acta radiol Ther Phys Biol* 6 (1967) 34
- NELSON A RÖNNBACK C et coll Influence of gestation and lactation on radiostrontium induced malignancies in mice II Retention of radiostrontium and relation between tumor incidence and excretion rate *Acta radiol Ther Phys Biol* 6 (1967) 129
- PARNLEY W W JENSEN J B and MAYS C W Skeletal self absorption of beta particle energy *In* Some aspects of internal irradiation p 437 Pergamon Press Oxford 1962
- STOKKE T Bone marrow reaction to local X irradiation p 167 Universitetsforlaget Oslo 1966
- VLASOV P A Reaction of the bone marrow to the influence of radioactive strontium *Radio-biologia* 4 (1964) 163

slow excretion phase may be considerably lower, if data for the male mouse apply to rats of both sexes. It has been shown by MULLER (1967) that the ^{90}Y daughter is rapidly transferred from the skeletally deposited ^{90}Sr to the testes. This leads on the one hand to an unexpected genetic dose contribution from ^{90}Sr — ^{90}Y (LUNING et coll. 1963) and on the other hand to a concomitant reduction of the bone marrow dose by about 70 per cent in the rat. This aspect is not revealed by whole body counting (COHN et coll. 1967, NILSSON et coll. 1967) or by the present radiochemical measurements, due to the reestablishment of the ^{90}Sr — ^{90}Y equilibrium post mortem.

SUMMARY

Bone marrow cellularity in the rat has been measured after injection of small amounts of ^{90}Sr . Reduced cellularity could be observed 6 and 12 weeks after injection of $1.5 \times 10^{-3} \mu\text{Ci/kg}$ leading to accumulated doses of 10 to 20 millirad.

ZUSAMMENFASSUNG

Die Zellenzahl des Knochenmarkes wurde nach Injektion kleiner Mengen von Strontium 90 in Ratten gemessen. Eine Reduktion der Zellenzahl wurde 6 und 12 Wochen nach der Injektion von $1,5 \times 10^{-3} \mu\text{Ci/kg}$ festgestellt, was einer akkumulierten Dosis von 10 bis 20 millirad entspricht.

RÉSUMÉ

Les auteurs ont fait des numérations des cellules de la moelle osseuse sur le rat après injection de petites quantités de ^{90}Sr . Ils ont observé une diminution du nombre des cellules six et douze semaines après l'injection de $1.5 \times 10^{-3} \mu\text{Ci/kg}$ de ^{90}Sr donnant une dose cumulative de 10 à 20 millirad.

REFERENCES

- ALEKSANDROVA M. F. and SEIVANOVA L. N. Reaction of the blood system of dogs upon chronic poisoning with strontium 90 depending on the original condition of hematopoiesis. *Radiobiologia* 3 (1963) 383.
- BOND U. P. and FEINENDEGEN L. E. ^3H thymidine ($^3\text{HTdR}$) incorporated into DNA: dosimetric and radiobiological considerations. In *Biophysical aspects of radiation quality*, p. 2. IAEA Technical Report Series No 58. Vienna 1966.
- COHN S. H. and GUSMANO E. A. Kinetics of strontium and calcium skeletal metabolism in the rat. *Proc. Soc. exp. Biol.* 126 (1967) 79.
- FORSBERG A. G. Studien über einige biologische Wirkungen der Röntgen- und γ Strahlen insbesondere am *Phycomyces blakesleeana*. *Acta radiol.* (1913) Suppl. No 49.
- LAMERTON L. F. Radiation biology and cell population kinetics. *Physics in Med. Biol.* 13 (1968) 1.

Table 1

Retention of ^{85}Sr in mothers — Figures give activity in per cent of initial measurement mean \pm SE (correction for decay)

Time between injection and measurement \pm 1	Days before start of lactation				Unmated control
	23	23	1		
1 week	36.6 \pm 1.47	36.7 \pm 0.96	33.6 \pm 1.00	26.0 \pm 1.10	37.7 \pm 2.24
1 month	24.7 \pm 0.86	19.2 \pm 0.70	17.7 \pm 0.60	14.6 \pm 0.96	26.6 \pm 0.53
2 month	12.5 \pm 0.78	10.2 \pm 0.65	9.4 \pm 0.37	10.2 \pm 0.52	18.2 \pm 0.39
3 months	10.3 \pm 0.74	7.6 \pm 0.42	7.4 \pm 0.18	7.9 \pm 0.47	18.5 \pm 0.50

* Males removed at times of birth

of about 70×10^3 cpm measured in the Small Animal Counter used in the experiment and described in an earlier paper (NELSON et al. 1965)

The interval between administration of radiostrontium and start of lactation in the different groups is shown in the schedule below which also gives the times when the animals were measured after the strontium administration

There were 20 mice in each group

Injection time
(before start of lactation)

41 days

23 days

23 days (males removed at
times of birth)

1 day

Unmated control

Interval between injection and
measurement

{ Zero time 1 week 1 month,
2 months and 3 months

In all groups but the control the females were mated to untreated CBA males with one female and one male in each cage. The males remained in the cages throughout the experiment except in the second of the 23 day groups. Here the male was removed 2 or 3 days before birth of the litter and was replaced about 10 days later. This was done in order to decrease the force of the breeding rate in this group. The females in the unmated control group were caged five together.

The measurements in the female mice are given as per cent of the initial value calculated for every individual. Correction has been made for decay by time. The results are given in Table 1 and Fig. 1.

INFLUENCE OF LACTATION ON RETENTION OF RADIOSTRONTIUM IN MICE

by

C. RONNBACK, A. NELSON and A. NILSSON

The influence of gestation and lactation on the induction of tumours by ^{88}Sr in mice was investigated by NILSSON (1967). He found that the latency period was extended and the bone tumour rate decreased in a mated group giving suck in comparison with an unmated group. These results initiated an investigation of the excretion rate of ^{88}Sr in groups of unmated mice, mated mice, and mated mice giving suck (NILSSON et al. 1967). The influence of gestation alone was negligible. Lactation, however, significantly decreased the retention. Since in their investigation the female mice were injected on different days of pregnancy only, supplementary data regarding the effect of lactation on retention when strontium was administered at different times before mating seemed desirable. In addition, further information on the amount of strontium transferred to the young via the milk should be obtainable.

Material and Methods Female CBA mice, aged about 70 days, were injected with 0.3 ml of a solution of ^{88}Sr in saline amounting to about 0.3 μCi per animal. The activity thus administered to the animals gave an initial value

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Table 1

Retention of ^{85}Sr in mothers — Figures give activity in per cent of initial measurement mean \pm SE (correction for decay)

Time between injection and measurement	Days before start of lactation				Unmated control
	41	23	23*	1	
1 week	36.6 \pm 1.47	36.7 \pm 0.96	33.6 \pm 1.00	26.0 \pm 1.10	37.7 \pm 2.24
1 month	24.7 \pm 0.81	19.2 \pm 0.70	17.7 \pm 0.60	14.6 \pm 0.96	26.6 \pm 0.53
2 months	12.5 \pm 0.78	10.2 \pm 0.62	9.4 \pm 0.37	10.2 \pm 0.52	11.2 \pm 0.39
3 months	10.3 \pm 0.74	7.6 \pm 0.42	7.4 \pm 0.18	7.9 \pm 0.47	11.5 \pm 0.50

*Males removed at times of birth

of about 70×10^3 cpm measured in the Small Animal Counter used in the experiment and described in an earlier paper (NELSON *et al.* 1965)

The interval between administration of radiostrontium and start of lactation in the different groups is shown in the schedule below which also gives the times when the animals were measured after the strontium administration

There were 20 mice in each group

*Injection time
(before start of lactation)*

41 days

23 days

23 days (males removed at
times of birth)

1 day

Unmated control

*Interval between injection and
measurement*

{ Zero time 1 week 1 month
2 months and 3 months

In all groups but the control the females were mated to untreated CBA males with one female and one male in each cage. The males remained in the cages throughout the experiment except in the second of the 23 day groups. Here the male was removed 2 or 3 days before birth of the litter and was replaced about 10 days later. This was done in order to decrease the force of the breeding rate in this group. The females in the unmated control group were caged five together.

The measurements in the female mice are given as per cent of the initial value calculated for every individual. Correction has been made for decay by time. The results are given in Table 1 and Fig. 1.

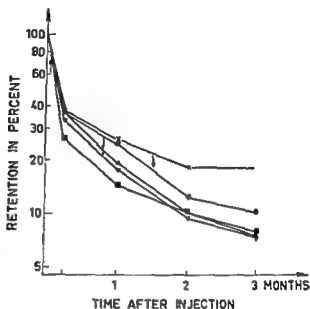


Fig. 1 Results of measurement of retention of ^{86}Sr in mice at different intervals before start of lactation ● 41 days ▲ 23 days ▼ 23 days (males removed at time of birth) ■ 1 day × unmated control

In addition to these measurements the activity in the young was measured at 1, 2 and 3 weeks after birth. The first and the second litters, and in group 4 also the third litter, were measured. The results are given as counts per minute and are shown in Table 2 and Fig. 2.

Results

The rate of excretion of ^{86}Sr from the female mice is shown in Table 1 and Fig. 1.

The unmated control females showed the highest retention, followed by the females which were injected 41 days before the start of lactation. As may be seen in Fig. 1, the excretion rate in the later group was enhanced at the start of lactation, the time of which is indicated by the arrow.

The females injected with strontium 23 days before start of lactation (i.e. 12 days before mating) show during the first month a higher excretion rate than those injected 18 days earlier. After the lactation had started, the excretion rate seemed to be of the same order of magnitude in these two experimental groups. As was described earlier, there also was one group of females, injected 23 days before the start of lactation, with a lower breeding rate. The retention in this group was somewhat lower than in the first mentioned 23 day group, though not statistically different.

The highest excretion rate occurred in females injected 1 day before start of lactation. Also in this group a very high excretion was noted after start

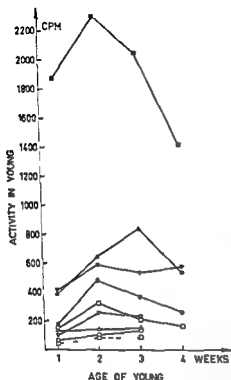


Fig 2 Results of measurement of the activity in the young mice at different interval before start of lactation ● 41 days ▲ 23 days ▼ 23 day (males removed at time of birth) ■ 1 day The black symbols indicate the first litter open symbol the second litter and the dotted line the third litter

of lactation in this case already during the first week. After one month the rate decreased and 3 months after injection the retention was practically the same as for the 23 day groups.

The strontium content in the young reflected the retention in their mothers, the content increasing with decreasing time between injection and start of lactation (see Fig 2 and Table 2).

There was in general however a great difference between the strontium content in the litters from females injected 1 day before start of lactation compared to those from females injected earlier during (or before) pregnancy. The retention in the young reached its highest point at the age of 2 weeks (in one group at 3 weeks). After that time suckling decreased and thus the strontium uptake via the milk. The retention curve shows a negative slope. After the 3 week measurement the young were weaned and given ordinary food. At this time a new litter usually was born in the first mentioned 23 day groups and within 24 hours the females were again made pregnant. In the

Table 2

Activity in young from mothers which had been injected with ^{85}Sr at different times before start of lactation — Measurements corrected for decay and given as counts per minute in thousands

Time for injection of mother	Age of young at time of measurement	Number of litters measured	Activity	
			In young ($\bar{x} \pm \text{SE}$)	In mothers ($\bar{x} \pm \text{SE}$)
41 days before lactation				
	<i>1st litter</i>			
	1 week	12	0.17 \pm 0.03	10.7 \pm 0.6
	2 weeks	11	0.18 \pm 0.03	7.6 \pm 0.7
	3 weeks	12	0.36 \pm 0.03	7.1 \pm 0.4
	4 weeks	11	0.26 \pm 0.02	6.7 \pm 1.1
	<i>2nd litter</i>			
	1 week	11	0.06 \pm 0.01	6.7 \pm 1.1
	2 weeks	8	0.10 \pm 0.01	7.1 \pm 0.7
	3 weeks	6	0.13 \pm 0.01	6.1 \pm 0.6
23 days before lactation				
	<i>1st litter</i>			
	1 week	17	0.39 \pm 0.01	13.3 \pm 0.1
	2 weeks	17	0.63 \pm 0.03	10.1 \pm 0.1
	3 weeks	17	0.81 \pm 0.01	8.8 \pm 0.3
	4 weeks	16	0.53 \pm 0.01	7.1 \pm 0.3
	<i>2nd litter</i>			
	1 week	13	0.13 \pm 0.03	7.1 \pm 0.3
	2 weeks	13	0.11 \pm 0.02	6.7 \pm 0.4
	3 weeks	12	0.15 \pm 0.01	6.4 \pm 0.6
23 days before lactation Males removed at times of birth				
	<i>1st litter</i>			
	1 week	11	0.40 \pm 0.01	12.5 \pm 0.3
	2 weeks	15	0.59 \pm 0.01	9.4 \pm 0.2
	3 weeks	11	0.53 \pm 0.01	8.3 \pm 0.1
	4 weeks	11	0.57 \pm 0.03	—
	<i>2nd litter</i>			
	1 week	1	0.10 \pm 0.01	—
	2 weeks	1	0.27 \pm 0.02	6.9
	3 weeks	2	0.23 \pm 0.12	3.6
1 day before lactation				
	<i>1st litter</i>			
	1 week	17	1.07 \pm 0.08	16.5 \pm 0.7
	2 weeks	17	2.25 \pm 0.10	12.9 \pm 1.0
	3 weeks	17	2.03 \pm 0.14	10.5 \pm 0.1
	4 weeks	17	1.10 \pm 0.06	9.0 \pm 0.1
	<i>2nd litter</i>			
	1 week	14	0.15 \pm 0.03	9.0 \pm 0.1
	2 weeks	14	0.32 \pm 0.03	8.2 \pm 0.1
	3 weeks	14	0.21 \pm 0.02	7.7 \pm 0.6
	4 weeks	13	0.16 \pm 0.02	6.0 \pm 0.3
	<i>3rd litter</i>			
	1 week	12	0.01 \pm 0.01	6.8 \pm 0.4
	2 weeks	10	0.09 \pm 0.03	6.3 \pm 0.4
	3 weeks	11	0.09 \pm 0.02	6.5 \pm 0.1

other 23 day group the females were not pregnant during the suckling period the mating occurring after the litter was weaned

Measurements in the second litter produced a similar picture with a lower strontium content than in the first litter. The differences between the groups also diminished.

The results of measurements in the young and corresponding values from the mothers measured on the same occasion, are presented in Table 2. It should be observed that the measurements in the first litter at the age of 4 weeks was made at the same time as the first week measurement in the second litter.

Comments It is apparent from our previous investigation (NILSSON et coll 1967) that in mice the gestation does not significantly enhance the excretion of radiostrontium administered before mating. KOLLMER & KRIEDEL (1965 a) found in rats however that the 48 hour retention of ^{86}Sr administered at the end of gestation was significantly lower than the 48-hour retention in virgin rats. Our present investigation, in which ^{86}Sr was administered 41 days and 23 days before partus confirmed that gestation does not influence the rate of excretion.

Lactation on the other hand was the important factor regarding enhancement of excretion of radiostrontium even when it was administered 41 days before lactation.

The stimulating effect of lactation on the metabolically active areas of the bone tissue primarily the epiphyse metaphyse regions seems to have caused this increased excretion as has also been shown by KOLLMER & KRIEDEL (1965 b).

As expected the uptake of strontium in the litters is dependent on the elapse of time between administration and partus. Due to the accumulation of strontium during the first week of lactation the greatest retention is measured at 2 weeks. After this time the suckling intensity decreases leading to a decrease of retention.

The fact that strontium such a long time after the administration can be mobilized from the bone tissue by a normal metabolic process constitutes a stimulation to further investigation of the underlying fundamental processes.

SUMMARY

The influence on the excretion rate of the interval between administration of radiostrontium and start of lactation was studied in CBA mice. The radionuclide ^{86}Sr was administered 41, 23 and 1 day respectively before start of lactation and the retention was studied during 3 months. The excretion rate decreased with increasing interval between administration and lactation. Even the group receiving radiostrontium 41 days prior to lactation displayed enhancement of the excretion rate during lactation.

ZUSAMMENFASSUNG

Der Einfluss des Zeitintervalles zwischen der Verabreichung von Radiostrontium und dem Beginn der Laktation auf die Ausscheidungsgeschwindigkeit wurde bei CBA Mäusen studiert. Das Radionuklid ^{85}Sr wurde bzw. 41, 23 und 1 Tag bevor dem Beginn der Laktation verabreicht und die Retention wurde während 3 Monaten observiert. Die Ausscheidung nahm mit zunehmendem Zeitintervall zwischen Verabreichung und Laktation ab. Auch die Gruppe die Radiostrontium 41 Tage bevor der Laktation erhielt wies eine Zunahme der Ausscheidungsrate während der Laktation auf.

RÉSUMÉ

Les auteurs ont étudié l'influence sur la vitesse d'excrétion de l'intervalle entre l'administration du strontium radioactif et le début de la lactation sur des souris CBA. Le radionucléide ^{85}Sr a été administré respectivement 41, 23 et 1 jour avant le début de la lactation et sa rétention a été étudiée pendant trois mois. La vitesse d'excrétion diminue à mesure qu'augmente l'intervalle entre l'administration du radionucléide et la lactation. Mais le groupe qui a reçu le strontium radioactif 41 jours avant la lactation a présenté une accélération de l'excrétion pendant la lactation.

REFERENCES

- NELSON A., RONNBACK C. and SJODÉN A. M.: Placental transfer of strontium 85 in mice. *Acta radiol. Ther. Phys. Biol.* 3 (1965) 477.
- NILSSON A.: Influence of gestation and lactation on radiostrontium induced malignancies in mice. I. Incidence, distribution and characteristics of ^{85}Sr induced malignancies. *Acta radiol. Ther. Phys. Biol.* 6 (1967) 33.
- NELSON A., RONNBACK C. et coll.: Influence of gestation and lactation on radiostrontium induced malignancies in mice. II. Retention of radiostrontium and relation between tumour incidence and excretion rate. *Acta radiol. Ther. Phys. Biol.* 6 (1967) 129.
- KOLLMEIER W. E. and KRIEGER H. (a): Retention of ^{85}Sr in lactating rats. *Nature* 205 (1965) 196.
- (b): Das biologische Verhalten von Radiostrontium bei Ratten im Verlauf der Laktation. *Int. J. Rad. Biol.* 9 (1965) No. 4.

RADIATION INDUCED INVOLUTION OF THE LYMPHATIC ORGANS OF THE YOUNG CHICKEN

by

JAMES L. MONTGOMERY

Thymic weight loss and splenic weight loss following whole body irradiation have been shown to be sensitive indicators of radiation damage (CARTER et coll 1950). The dose dependence of these responses has made them a valuable measure of the relative biologic effectiveness (RBE) of mixed radiations or of radiations of unknown quality (CARTER et coll 1950 HARRIS et coll 1952 HARRIS et coll 1953). The thymus and the spleen are similarly radiosensitive in various mammals despite widespread differences in the radiosensitivity of the species as measured by the 30-day lethality (BLOOM 1954).

Three major lymphatic organs are found in the chicken: the thymus, the bursa of Fabricius, and the spleen. The thymus and the spleen are analogous to the mammalian thymus and spleen, but the bursa is apparently a uniquely avian organ. JOLLY (1913) reported involution of both the thymus and the bursa following whole body roentgen irradiation, and JACQUEZ & KARNOFSKY (1950) and ATKINSON et coll (1961) described histologic changes in the lympho-

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epithelial organs of the chicken similar to those observed following whole body irradiation of the mouse. None of the studies reported to date, however, have quantitatively examined the acute involution of the lymphatic organs of the chicken following graded doses of radiation.

This study was designed to examine both the radiation dose sensitivity of the chicken's lymphatic tissues and the time pattern of involution following single exposures to roentgen radiation. Since early radiation mortality in the young chicken is acutely sensitive to dose rate, or total exposure time (STEARNER et coll. 1957), the dose rate sensitivity of the chicken's lymphatic tissues was also examined. Comparable radiation exposures were performed at both a low rate (8.8 R/min) and a high dose rate (96.5 R/min).

Materials and Methods

Exposure conditions The source of radiation was a conventional therapy machine operated at 250 kVp and 15 mA with 0.5 mm Al and 1.0 mm Cu added filtration. The first half-value layer, as measured 55 cm from the target, was 1.6 mm of Cu. Exposures measured with a commercially calibrated Victoreen Condenser R-Meter were 0 R, 50 R, 100 R, 200 R, and 400 R.

High dose rate (HDR) Groups of 16 chicks were exposed in a cylindrical polyethylene chamber 24.75 cm (9 3/4 inches) in diameter and 4.45 cm (1 3/4 inches) in height, which was rotated in the radiation field at approximately 2/3 RPM. At a distance of 55 cm from the radiation source, the dose rate measured under the conditions of maximum backscatter at the midpoint of the exposure chamber was 96.5 R/min. A decrease in dose of less than 5% was observed at the perimeter of the exposure field.

Low dose rate (LDR) Groups of 20 chicks were exposed in a cylindrical cardboard chamber 32 cm (12.5 inches) in diameter and 7.6 cm (3.0 inches) in height, which was rotated at approximately 2/3 RPM. At a distance of 185.4 cm from the target, the dose rate measured under conditions of maximum backscatter was approximately 8.8 R/min. A difference of less than 1% was found between the doses measured at the midpoint and at the periphery of the exposure chamber.

Animals Single comb white leghorn cockerels obtained from Kluger Hatchery, Saline, Michigan, shortly after hatching were housed 50 per shelf in a standard chick brooder. Purina starter mash and water were available ad libitum. Radiation exposures were performed on the tenth day of age. Because the

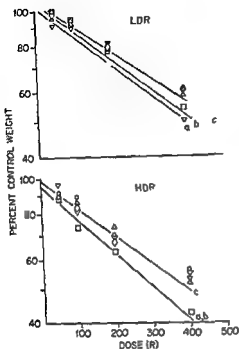


Fig 1 Lymphatic tissue dose response to low dose rate and high dose rate roentgen irradiation. Total lymphatic tissue following exposure to 0 R, 50 R, 100 R, 200 R or 400 R at either 8.8 R/min (LDR) or 96.5 R/min (HDR). At each dose the total lymphatic tissue is plotted for the 5 days following exposure: ○ day 1, □ day 2, △ day 3, ▽ day 4, ◇ day 5. Three lines have been drawn through the sets of points at each dose: the points of maximum depression at each dose (a), the points of maximum 1—2 day depression (b), and the average of all points at each dose (c). In the case of the high dose rate (HDR) exposures the first two lines (a, b) are the same.

Lymphatic tissues of the chick like those of mammals are sensitive to adrenal corticoid release following stress (GARREN et coll 1956, NEWCOMER et coll 1966). Three control groups were maintained. Two groups were handled as high dose rate and low dose rate animals, respectively, and the third group was maintained as an unstressed cage control. The lymphatic organ weights of both stressed control groups were reduced by approximately 5% as compared to those of the cage controls. All animals including the experimental control series were retained in their exposure chambers for a period of time equal to that of the longest exposure.

Dissection. For 5 days following exposure a minimum of 8 chicks per exposure group were killed daily and the thymus, bursa and spleen removed from each. The organs were immediately cleaned of extraneous tissues and their wet weights determined to the nearest 0.1 mg. Because a direct relationship exists between lymphatic organ weight and body weight in the young chicken, absolute organ weights were converted to mg/100 g body weight. Since even the young chicken is capable of retaining several grams of food in its crop, the

Table 1

Response of chick lymphatic tissue to HDR and LDR roentgen exposures — Values derived from Fig. 1

	ED ₅₀		Slope		y intercept		Slope LDR
	LDR	HDR	LDR	HDR	LDR	HDR	Slope HDR
All points	475 R	395 R	0.113	0.125	106 %	98 %	0.85
Max involution (1—2 d)	410 R	305 R	0.128	0.140	105 %	95 %	0.91
Max involution (1—3 d)	400 R	305 R	0.128	0.140	102 %	95 %	0.91

Comparison of the slopes of the dose response lines indicates that exposure at a low dose rate (LDR) was only 85 % to 91 % as effective per roentgen in producing lymphatic involution as exposure at a high dose rate (HDR). In addition the y intercepts of the HDR lines were below those of the comparable LDR lines.

Table 2

Total lymphatic tissue weight following irradiation

Dose	Dose rate	Total lymphatic tissue weight (mg/100 g bw)				
		Day 1	Day 2	Day 3	Day 4	Day 5
0 R		858 (83)	935 (89)	988 (102)	1049 (107)	1084 (117)
50 R	LDR	849 (84)	926 (88)	948 (94)	955 (112)	1062 (122)
	HDR	781 (83)	823 (92)	899 (104)	1018 (111)	965 (117)
100 R	LDR	781 (83)	888 (89)	929 (94)	944 (109)	1019 (114)
	HDR	764 (85)	692 (85)	850 (91)	850 (109)	900 (114)
200 R	LDR	609 (78)	734 (83)	771 (94)	850 (103)	856 (107)
	HDR	601 (83)	589 (89)	721 (98)	713 (104)	726 (120)
400 R	LDR	515 (80)	505 (85)	573 (91)	514 (97)	650 (106)
	HDR	476 (81)	402 (84)	514 (91)	556 (97)	607 (108)

Control values (0R) are the averages of 16 measurements each; all other values are averages from 8 measurements each. Average body weight in grams is shown in parentheses.

Animals to be dissected each day were removed from the brooder before feeding began in the morning. Any food found in the crop was removed before body weight measurements were taken.

Results

The dose response of the chick lymphatic tissues to irradiation is presented in Fig. 1. Each point represents the average total lymphatic tissue weight of eight birds expressed in percentage of the value of the stressed control.

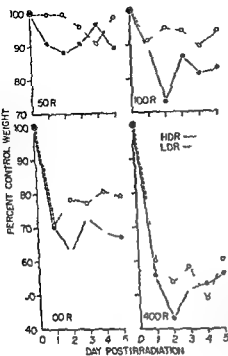


Fig. 2 Daily pattern of involution following roentgen irradiation. Exposures to 50 R, 100 R, 200 R or 400 R at 8.8 R/min (broken lines) were less effective in producing lymphatic tissue involution than were comparable exposures at 96.5 R/min (solid lines).

groups. Three lines have been drawn through the two sets of points: (a) through the points of maximum depression at each dose; (b) through the points of maximum 1–2 day depression; and (c) through the average of all points. In the case of the high dose rate exposures, the lines (a) and (b) are the same. The organ weights following both high dose rate and low dose rate exposures are well described by either a linear or a log linear relationship with linear dose. The latter representation was chosen since it is typical of the response of cell populations to increasing radiation doses.

The negative slopes, y intercepts, and ED_{50} values obtained from the lines in Fig. 1 are given in Table 1. The differences in slopes indicate that exposure at the low dose rate was 0.85 to 0.91 as effective per R as exposure at the high dose rate in producing lymphatic involution. The ED_{50} values obtained either directly or by extrapolation of the lines in Fig. 1 varied from 305 R (maximum involution) to 395 R (all points) for the high dose rate exposures and from 400 R (maximum involution) to 475 R (all points) for the low dose rate exposures. The y intercepts of the HDR lines were 7% to 10% below the comparable LDR lines.

The changes in organ weights as a function of time after exposure (in days) are given in Table 2 and Fig. 2 for each of the four exposures. Except at 50 R, where no decrease was seen following LDR exposure until the third or fourth day after exposure, the weight loss was similar for both exposure conditions on the first day after exposure, on the second day an additional decrease was seen in the weights of the lymphatic tissues in the high dose rate groups, while little or no further decrease was seen in the low dose rate groups.

Discussion

Dose response The rate of acute involution of the chick lymphoepithelial organs (Fig. 2) was similar to that reported for mammals after a single acute exposure to irradiation (KALLMAN et al. 1955). Maximum initial depression was reached by the first or second day after exposure and was followed by varying degrees of recovery or additional secondary injury. Measured at the time of maximum depression, the ED_{50} values were 305 R (HDR) and 400 R (LDR). These doses were three to four times greater than those reported to produce 50% involution of the mouse thymus and spleen measured at maximum depression. On the fifth day after exposure, when recovery is apparent in both the mouse and the chick, the ED_{50} values are increased to 150–210 R in the mouse and to 395 R (HDR) and 475 (LDR) in the chick, the values in the latter species are still a factor of more than two higher than those in the former.

The following points should be considered with respect to the use of acute involution of chick lymphoepithelial organs for the bioassay of mixed or unknown radiations.

1. A linear dose versus log organ weight response is available on the first to second post irradiation day. Unpublished observations indicate that this relationship is maintained at least through 600 R of whole body irradiation.

2. Should different exposure groups be subjected to different degrees of stress, newly hatched chicks may be used for the assay. In these animals the pituitary-adrenal axis is incompletely developed, and external stress has a minimal effect on lymphatic organ weight.

3. Above 650 R of acute (dose rate greater than 10 R/min) whole body irradiation, chicks begin to die in the early period (within 48 hours post exposure), complicating measurements at and above this dose.

4. Although the dose sensitivity is not as great in the chick as in the mouse, the larger amount of lymphatic tissue in the chick and the greater amount of tissue remaining, particularly after doses of 400 to 600 R, make possible accurate dose estimates even with small numbers of animals.

Dose rate response Measured at the ED₅₀ values the low dose rate exposures were 0.74 (maximum involution) to 0.89 (average of all points) as effective as high dose rate exposures in producing lymphatic tissue involution. A portion of the difference observed by this measure was the result of the difference in the y intercepts of the lines obtained from the two exposure conditions. As measured by differences in the slopes of the lines in Fig. 1, low dose rate exposure was still 15 % to 10 % less effective per roentgen than high dose rate exposure in producing acute involution of the chick lymphatic tissues. This difference was primarily the result of additional involution in the high dose rate animals on the second day after exposure following the nearly equal involution in the two groups observed on the first day after exposure. This difference was generally maintained thereafter throughout the 5 day experimental period.

The observed dose rate effect can be explained by one or both of the following possibilities. First the direct killing of the radiosensitive lymphocytes in the thymus, bursa, and spleen is a dose rate dependent event. Second the high dose rate exposures initiate events outside the lymphatic tissues which by indirect or abscopal processes cause killing of lymphocytes in these organs in addition to the direct damage from either high or lower dose rate exposures.

Neither of these possibilities is excluded by the data presented in this experiment. Although no evidence has been reported concerning a dose rate effect on lymphatic organ weights, dose rate effects have been reported for a variety of endpoints in mammals (BATEMAN et coll 1962, CURTIS et coll 1964, RUSSELL 1965). In no case, however, is the dose rate effect as great as that reported here for comparable dose rates. On the other hand, in addition to the striking dose rate effect previously mentioned for early (48 hour) mortality in the chicken (JACQUEZ et coll 1950), a dose rate effect on 3 to 30 day mortality has also been reported which is comparable in magnitude to that reported here (TYLER et coll 1962). The early appearance of the effect only two days after exposure is consistent with a dose rate sensitivity of the radio sensitive lymphocytes themselves.

Partial body exposures (MONTGOMERY 1967) have revealed an early (2 day) abscopal effect on the chick lymphatic organs which appears to be related to the highly dose rate dependent 48 hour mortality. Exposures performed at 40 R/min have produced results similar to those reported here for exposure at 100 R/min. It would seem quite possible then that even at sublethal doses damage of the type responsible for dose rate dependent mortality in the chick is being accumulated and that this damage indirectly contributes to the lymphatic involution following high dose rate exposures.

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- GARREN H W and SHAFFNER C S How the period of exposure to different stress stimuli affects the endocrine and lymphatic gland weights of young chickens Poultry Sci 35 (1956) 260
- HARRIS P S and BRENNAN J T The biological effectiveness of thermal neutrons determined by the decrease in weight of the spleen and thymus of the mouse Los Alamos Scientific Laboratory Report LA 1410 May 1952
- and ELLINWOOD L E Biological effectiveness of 14 MeV neutrons Spleen and thymus weight loss in mice as the biological indicator Los Alamos Scientific Laboratory Report LA 1629 December 1953
- JACQUEZ J A and KARNOWSKY D A The toxicity and pathological effects of roentgen rays in the chicken Amer J Roentgenol 64 (1950) 289
- JOLLY J Modifications de la bourse de Fabricius à la suite de l'irradiation par les rayons X Comp Rend Soc Biol 75 (1913) 120
- KALLMAN R F and KOHY H I The reaction of the mouse thymus to X rays measured by changes in organ weight Radiat Res 2 (1955) 280
- MONTGOMERY J L Abscopal radiation damage to the chick thymus and bursa of Fabricius Radiat Res 31 (1967) 599
- NEWCOMER W S and CONNALLY J D The bursa of Fabricius as an indicator of chronic stress in immature chickens Endocrinology 67 (1966) 264
- RUSSELL W L Studies in mammalian radiation genetics Nucleonics 23 (1965) 53
- STEARNER S P and TYLER S A An analysis of the role of dose and dosage rate in the early radiation mortality of the chick Radiat Res 7 (1957) 253
- TYLER S A and STEARNER S P Discrimination among injury processes reflected in acute radiation mortality Int J Rad Biol 4 (1962) 493

SUMMARY

Ten day old leghorn cockerels were exposed to 50 R 100 R 200 R or 400 R of roentgen rays at either 8.8 R/min or 96.5 R/min. Determinations of the combined weights of the thymus bursa of Fabricius and spleen were made for the ensuing 5 days. Maximum depression of the weights of these organs were obtained 1 day after the low dose rate exposures and 2 days after the high dose rate exposures. Measured 5 days after exposure the combined lymphatic organ weights were reduced 50% by 395 R when the dose rate was 96.5 R/min.

ZUSAMMENFASSUNG

Röntgenbestrahlung von 10 Tage alten weissen Leghorn Hähnen wurde bei 50 R 100 R, 200 R oder 400 R vorgenommen, entweder mit 8,8 R/min oder 96,5 R/min. Gesamtgewicht bestimmung von Thymus Bursa Fabricius und Milz wurde während den folgenden fünf Tagen unternommen. Die maximale Herabsetzung des Gewichtes dieser Organe wurde bei der niedrigen Dosisbestrahlung nach einem Tag und bei der hohen Dosisbestrahlung nach zwei Tagen beobachtet. Am fünften Tag nach der Bestrahlung mit 395 R war das Gewicht der lymphatischen Organe um 50% vermindert, wenn die Doserate 96,5 R/min war.

RÉSUMÉ

De jeunes coqs leghorn blancs âgés de 10 jours ont été exposés à des doses de 50 100 200 ou 400 R de rayons roentgen à des débits de 8.8 R/minute ou de 96.5 R/minute. Le poids total du thymus de la bourse de Fabricius et de la rate a été déterminé pendant les 5 jours suivant l'irradiation. Le poids de ces organes atteint un minimum un jour après les irradiations à fort débit. Le poids total des organes lymphatiques mesuré 5 jours après l'exposition aux radiations est réduit de 50% par une dose de 395 R quand le débit de dose est de 96.5 R/minute.

REFERENCES

- ATKINSON R. L., QUISENBERRY J. H., MEDLEY A. H. and BERGER G. The effect of whole body γ irradiation on the blood and other tissues of white leghorn cockerels. *Health Phys.* 6 (1961) 163.
- BATEMAN J. L., BOND V. P. and ROBERTSON J. S. Dose rate dependence of early radiation effects in small mammals. *Radiology* 79 (1962) 1008.
- BLOOM W. Histological changes after irradiation. *Radiation biology*, p. 1104. Edited by A. Hollaender. Vol. 1 part II. McGraw Hill Book Co. New York 1954.
- CARTER R. E., HARRIS P. S. and BRENNAN J. T. The effect of acute doses of γ irradiation on the splenic and thymic weight of CF 1 female mice. Los Alamos Scientific Laboratory Report LA 1075. March 1950.
- CURTIS H. J., TILLEY J. and CROWLEY C. The cellular differences between acute and chronic neutron and gamma ray irradiation in mice. Biological effects of neutron and proton irradiations. Vol. II, p. 143. International Atomic Energy Agency, Vienna 1964.

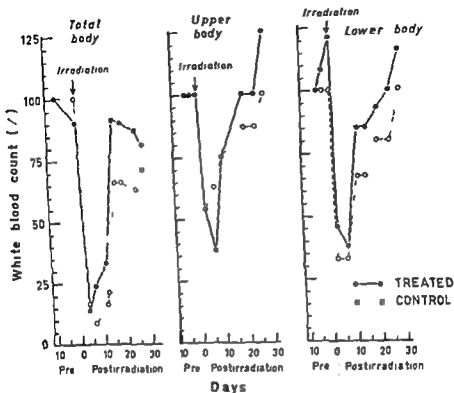


Fig 1 Effect of testosterone treatment on total upper and lower body irradiated rats

Material and Methods Male rats of the Hebrew University strain ranging in weight from 200 to 250 g were fed water and food pellets ad libitum. Hypophysectomy was carried out by the parapharyngeal approach. Total body exposures of 300 and 500 R and localized doses of 500 and 1 000 R were given at a dose rate of 130 R/min at 200 kV (15 mA) with filters of 0.5 mm Cu and 1.0 mm Al. Animals exposed to localized irradiation were anesthetized with intraperitoneal sodium pentobarbiton (30 mg/kg). Blood samples for the leucocyte count were obtained from the tail. The results were expressed as the average of all determinations for a group of rats treated alike. The initial value was called 100%. Testosterone propionate was administered to one group in daily subcutaneous doses of 5 mg and to another group in daily doses of 0.5 mg per rat from a week before irradiation and during the whole experiment. Five different sets of experiments were performed.

In the first experiment 50 rats received total body irradiation. 25 of them

EFFECT OF TESTOSTERONE TREATMENT AND HYPOPHYSECTOMY ON THE LEUCOCYTE COUNT IN IRRADIATED RATS

by

E. ROBINSON and I. CHOWERS

The androgenic hormone, testosterone, when used in large doses stimulates erythropoiesis, primarily by a direct effect on early cell precursors (KENNEDY et coll 1957, MIRAND et coll 1965, SHAHIDI et coll 1961). The possibility that this hormone may increase white blood cell production has been suggested (KENNEDY 1962, KENNEDY et coll 1956) and later confirmed by BRODSKY et coll (1964). These investigators reported that pretreatment of three cases of carcinoma with testosterone prevented significant granulocytopenia after the administration of cytotoxic agents.

In order to elucidate the mechanism of the action of testosterone, total and partial body irradiated rats were treated with this hormone and the leucocyte counts compared with those of irradiated but otherwise untreated rats.

The purpose of the present study was also to observe the effect of hypophysectomy on partial and total body irradiated rats and to evaluate the effect of testosterone on the leucocyte count in hypophysectomized and irradiated rats.

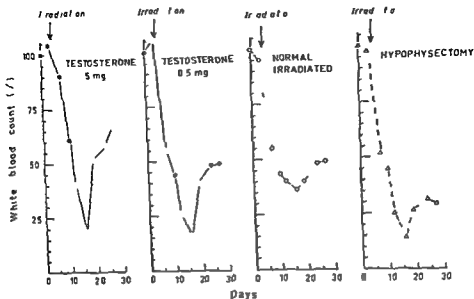


Fig 3 Effect of hypophysectomy and testosterone treatment on irradiated rats

upper body irradiation (from the xyphoid process up to and including the skull) and 16 rats were subjected to lower body irradiation (caudal to the xyphoid process). In each experiment of this set, half the number of rats had undergone upper body irradiation, half the number of the lower body irradiated rats had been hypophysectomized, and half the number not. A group of hypophysectomized non irradiated rats served as control group.

In each experiment the findings in the merely hypophysectomized and in the hypophysectomized and testosterone treated groups were compared with those in the simultaneously performed control experiments. The differences between the treated rats and the control animals were examined by the Van ELTEREN'S (1960) method of combining independent Wilco tests from the various experiments and the F test.

Results

The results are presented in Figs 1, 2, and 3. It may be seen that the recovery of the leucocyte count was faster in the testosterone treated groups than in the controls. This difference was statistically significant $Z = 0.00064$. No

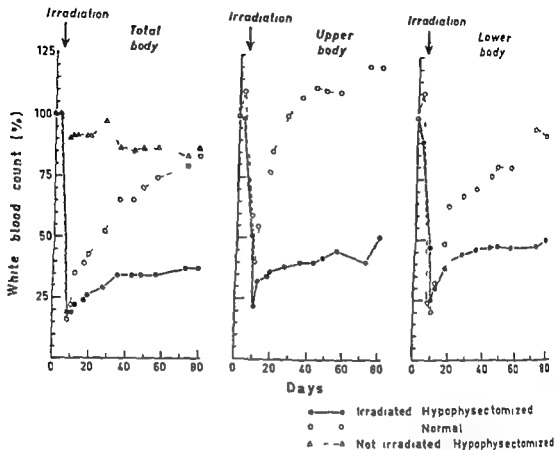


Fig. 2 Effect of hypophysectomy on the white blood count in irradiated rats

were treated with testosterone and 25 served as controls. Testosterone administration began a week prior to irradiation and was continued up to the end of the experiment.

Each of the other two experimental groups consisted of 20 rats, 10 of which received upper body irradiation (from the xyphoid process up to and including the skull) and 10 rats lower body irradiation (caudal to the xyphoid process). In each experiment, half the number of the upper body irradiated and half the number of the lower body irradiated rats were treated with testosterone, the remainder serving as controls.

In the fourth set of experiments, 40 rats were exposed to total body irradiation, of which 10 had been previously hypophysectomized and these received 5 mg testosterone daily, 10 had been hypophysectomized and got 0.5 mg testosterone, 10 had been hypophysectomized and received no further treatment, and 10 were not subjected to operation (controls).

The last set of experiments included 32 rats, 16 of which were exposed to

that irradiation of adrenalectomized rats provokes less drop and quicker increase in the leucocyte count than the irradiation of normal rats. The present results indicate that the relative drop in the white blood count in hypophysectomized and normal irradiated rats is similar.

Measurement of the response after irradiation disclosed that the quickest recovery was in the 5 mg testosterone treated rats followed by the 0.5 mg testosterone treated group and then the non operated group with the lowest recovery in the hypophysectomized rats. It therefore appears that hypophysectomized rats have some impairment in their ability to recover after irradiation. Testosterone is apparently able to correct this delay in the recovery of the leucocyte count. It is not clear why hypophysectomized rats exhibit some delay in recovery. It is obvious, however, that hypophysectomy depresses erythropoiesis. Testosterone has also the power to stimulate leucopoiesis in normal irradiated rats. The present experiments have shown the same effect in hypophysectomized rats.

This work suggests the advisability of administering chemotherapy before hypophysectomy in cases of mammary carcinoma. If this is not feasible, testosterone treatment would seem to be indicated. Further clinical trials are obviously required.

SUMMARY

Normal and hypophysectomized rats were treated by total and partial body irradiation and testosterone propionate. It would appear that some impairment occurs in the restoration of the leucocyte count following irradiation in hypophysectomized rats and that testosterone is able to correct this disturbance.

ZUSAMMENFASSUNG

Normale Ratten und Ratten bei denen die Hypophyse exstirpiert war wurden mit Ganzkörper bzw. partieller Bestrahlung und mit Testosteronpropionat behandelt. Es scheint als ob bei den Tieren ohne Hypophyse die Normalisierung der Leukocytenzahl nach der Bestrahlung verzögert wurde und dass bei einer Verabreichung von Testosteron diese Störung korrigiert werden kann.

RÉSUMÉ

Des rats normaux et des rats hypophysectomisés ont été traités par irradiation totale ou partielle du corps et par le propionate de testostérone. Il semble que le retour à la normale du nombre des leucocytes après irradiation se fait plus difficilement chez les rats hypophysectomisés et que la testostérone peut remédier à cette perturbation.

difference was noted between the treated and untreated groups in the maximum decrease in leucocyte count after irradiation.

In the partial body treated groups the decrease in leucocyte count after irradiation was less, and its increase was more rapid in the upper body irradiated than in the lower body irradiated animals. These differences proved however insignificant. In both groups the rise in leucocyte count was more rapid in the testosterone treated than in the corresponding untreated group.

The following points were investigated in the last two sets of experiments: (1) the initial drop in the leucocyte count after irradiation, (2) the increase in leucocytes between the lowest count and that present 2 weeks after irradiation, and (3) the difference between the pre irradiation value and that at the end of the experiment.

The initial absolute drop in the leucocyte count was greater in the hypophysectomized and irradiated rats than in the non operated irradiated group, $P = 0.001$. Measurement of the relative decrease revealed however no difference between the groups. This discrepancy is due to the fact that the pre irradiation leucocyte count in the hypophysectomized rats was higher. In all the groups exposed to total body irradiation, the difference between the lowest count and that obtained two weeks later indicated that it was least in the irradiated operated group and increased in the other groups according to the following order: non operated and irradiated, irradiated plus testosterone 0.5 mg, hypophysectomized and irradiated, and testosterone 5 mg. All these differences were statistically significant, $P = 0.01$. When the difference between the pretreatment value and that obtained at the end of the experiment was compared in the four groups undergoing total body irradiation, it was evident that the smallest difference was in the operated plus testosterone 5 mg group, followed by the group of operated plus testosterone 0.5 mg, the non operated, and lastly the operated group. The differences between the groups were significant, $P = 0.01$. In the partial body irradiated rats there was a quicker recovery in the leucocyte count for the upper body irradiated than in the lower body irradiated group. In the hypophysectomized upper or lower body irradiated rats, the leucocyte count recovery was slower than in the corresponding control.

Discussion

Hypophysectomy in carcinoma of the breast in human subjects is a well established method of treatment. However, it is not known if the white blood count reacts differently to radiotherapy and chemotherapy in hypophysectomized cases compared to others. HOCIMAN *et coll.* (1961) have reported

EFFECTS OF RADIATION DAMAGE TO BONE MARROW ON SUSCEPTIBILITY OF CHICKS TO ERYTHROLEUKEMIA VIRUS

by

C H CHU and B LAGERLOF

Studies of fowl and murine virus-induced leukemias indicate that several host factors are responsible for the susceptibility. Increasing immunologic maturity of the host and increasing cellular differentiation together with decreasing proliferative activity of the target cells are associated with decreasing susceptibility to virus action in some systems (LAGERLOF & SUNDELIN 1963). In murine leukemia systems the response of the animal to the virus can be markedly enhanced by roentgen irradiation or by urethane which cause damage and subsequent regeneration of the thymus, the target organ of the virus (KAPLAN 1967; HARAN-GIERA & KAPLAN 1964).

The present investigation was undertaken with a view to determine whether the pathogenic effect of the fowl erythroleukemia virus can be altered by modifying the cellularity and the degree of cellular differentiation of the target, i.e. the bone marrow. Bone marrow changes were produced by exposing the chicks to whole body irradiation. The sequential changes in the bone marrow after irradiation were followed in a pilot study. Based on this experiment a study was

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REFERENCES

- BRODSKY I, DENNIS L H and KAHN S H Testosterone enanthate as a bone marrow stimulant during cancer chemotherapy Preliminary report Cancer Chemother Abstr 34 (1964), 59
- ELTEREN VAN Ph On the combination of independent two sample tests of Wilcoxon Bull Inst int Stat 37 (1960) 351
- HOCHMAN A, FEIGE Y and STEIN J A The effect of X irradiation on peripheral blood leukocytes in normal and adrenalectomized rats Radiat Res 15 (1961), 15
- KENNEDY M J Stimulation of erythropoiesis by androgenic hormones Ann intern Med 57 (1962), 917
- and GILBERTSON A S Increased erythropoiesis induced by androgenic hormones J clin Invest 35 (1956), 717
- — Increased erythropoiesis induced by androgenic hormone therapy New Engl J Med 256 (1957) 719
- MIRAND E A GORDON A S and WENTO J Mechanism of testosterone action in erythropoiesis Nature 206 (1965), 270
- SHAHIDI N T and DIAMOND L K Testosterone induced remission in aplastic anemia of both acquired and congenital types New Engl J Med 264 (1961), 953



Fig 1 Acute irradiation damage of bone marrow at 4 days. Edema and few viable erythrocytes (centre) in the necrotic marrow. Hematoxylin eosin $\times 250$.

Fig 2 Acute irradiation damage with edema and cellular necrosis 4 days after irradiation. Persisting erythropoietic activity in some islands (bottom). Hematoxylin eosin $\times 350$.

been recorded in tables. In addition, the susceptibility to the virus has been calculated according to

$$\sum \frac{1}{t}$$

where t is the latent period from virus inoculation to death and N is the corrected number of virus-inoculated chicks

Experimental groups. Chicks were exposed to a single dose of 600 rad in one experiment (1) intended for the evaluation of radiation damage to the bone marrow. The chicks were killed by decapitation 4, 8, 12 and 20 days after irradiation and all marrow in both femora and tibiae was collected separately for histologic examination. Four to six untreated normal chicks of corresponding ages furnished the control material.

performed on the pathogenic effect of the erythroleukemia virus inoculated in the chicks, in the successive phases of post irradiation damage and regeneration of the bone marrow

Material Random bred white Leghorn chicks (Vanhammar, Vansbro) were used throughout. They were kept in artificially heated cages with free access to commercial chick feed and water, irradiated and non irradiated chicks were kept in separate cages but otherwise the conditions were the same.

The properties of the erythroleukemia virus and the disease evoked by it have been described in detail earlier (LAGFLOF 1960). The source of the virus was a lyophilized pool of medium from cultures of erythroleukemic bone marrow, diluted to the original volume with distilled water. The dose was 0.2 ml intravenously.

Irradiation The chicks were exposed to a single dose of 600 rad unfiltered ^{60}Co , the exposure time being 19 minutes and the source target distance 150 cm. The irradiation resulted in about 10 per cent mortality within the first two days. The preliminary pilot studies had indicated that this dose caused considerable damage to the marrow in spite of the low mortality rate.

For *bone marrow biopsy* the right femur was exposed under general anesthesia, and a hole of 2 mm diameter was drilled through the cortex of the bone into the medullary cavity. A piece of bone marrow, about 5 mm in length, was aspirated through a needle of 1 mm diameter. The hole was covered with muscular tissue and the operation area closed with silk.

Histologic examination Bouin's fixative was used for the biopsy material of bone marrow and other tissues collected for histologic examination. Ordinary paraffin sections were prepared and stained with hematoxylin-eosin.

All histologic sections were coded and the examination was made without knowledge of the time of the irradiation treatment. The control marrows were also included, as coded histologic sections, in the experimental material.

Necrosis and edema, indicative of recent damage, were registered as well as increased fat infiltration with decreased cellularity and signs of erythroid or myeloid regeneration. All these findings were semi quantitatively registered according to a 4+ scale where 0 denoted normal findings, 1 or 2+ slight to moderate changes, and 3 or 4+ severe changes.

The obtained biopsy material was sometimes too small to permit a reliable histologic examination. These specimens were excluded when calculating the virus activity figures in the various groups in Table 2.

Calculation of virus activity The number of chicks dying from leukemia versus number of virus inoculated chicks corrected for intercurrent deaths, have



Fig 5 Aplastic bone marrow 0 days after irradiation Hematoxylin-eosin $\times 350$

Fig 6 Low power view Persistent edema and patchy necrosis of bone marrow 90 days after irradiation Hematoxylin-eosin $\times 100$

Results

Evaluation of radiation damage to bone marrow

Four days after irradiation The changes at microscopy of the bone marrow 4 days after irradiation with 600 rad were uniform in type although the degree differed. All samples exhibited moderate to marked necrosis haemorrhage and edema associated with hypocellularity and marked depression of the hematopoietic activity (Fig 1). Slight erythropoietic activity was evident in some areas (Fig 2).

Eight days after irradiation Necrosis of the bone marrow was still a common finding 8 days after irradiation. Haemorrhage and edema were present to about the same degree as in the 4-day group. The changes were generally associated with increased fat infiltration in the marrow and more or less complete aplasia in large areas. Usually only the peripheral parts of the marrow presented hematopoietic activity (Fig 3). The marrow from one of the four chicks exhibited



Fig 3 Hypoplastic bone marrow with increased fat content 8 days after irradiation. Slight myeloid activity with two sinusoids presenting moderate erythropoietic activity. Hematoxylin eosin $\times 250$.

Fig 4 Sinusoid with moderate erythropoietic activity 12 days after irradiation. Slight myeloid activity in the extrasinusoidal tissue is also evident. Hematoxylin eosin $\times 350$.

Groups of twelve 1 day old chicks were in another experiment (2) exposed to 600 rad and bone marrow biopsy was performed 2, 8 and 20 days after irradiation. Following biopsy, the chicks were inoculated with erythroleukemia virus. Histologic examination of the bone marrow, spleen and liver was performed in all the chicks that died of leukemia or were killed at the termination of the experiment, 60 days after inoculation. Corresponding groups of non irradiated chicks constituted the control material. The control groups were virus inoculated at the same time as the experimental groups.

All the groups were kept for 2 months and then the remaining chicks were killed and examined.

Intercurrent deaths Five out of a total of 72 chicks, in the experimental and control groups, died intercurrently before leukemia had developed. These five chicks were excluded from any further calculations.

Table 2

Correlation of erythroleukemia virus activity with the degree of radiation marrow damage (A) and evidence of erythroid regeneration (B)

	Number of dead versus number of inoculated	$\sum \frac{1}{n}$
A		
Irradiated chicks with advanced marrow damage (3 and 4+)	4/13	0.075
Irradiated chicks with slight marrow damage (1 and 2+)	17/21	0.092
B		
Irradiated chicks with histologic evidence of erythroid regeneration	17/25	0.062
Irradiated chicks without histologic evidence of erythroid regeneration	4/9	0.076
All irradiated control chicks	22/33	0.063

The incidence of leukemia at corresponding ages was almost identical in the experimental groups and the control groups. The susceptibility of the chicks as calculated according to

$$\sum \frac{1}{n}$$

was identical in the experimental groups and the control groups at 2 days and 20 days after irradiation. At 8 days the control group had a slightly higher susceptibility.

The biopsies revealed that these experimental groups differed from the above mentioned groups by having greater intra group variations of radiation damage. Thus some of the chicks that were inoculated with virus 20 days after irradiation had persistent widespread cellular necrosis of the marrow or aplasia with marked fatty infiltration (Fig. 6). Placing the birds according to the presence of severe marrow damage and advanced hypocellularity into one group (3 and 4+) and those according to the presence of slight to moderate necrosis or hypocellularity into another (1 and 2+) irrespective of the time of virus-inoculation gave the figures recorded in Table 2.

The chicks with severe marrow damage histologically classified as 3 or 4+ had markedly reduced susceptibility for the virus and only four out of thirteen chicks developed leukemia. Of the twenty-one chicks with slight or moderate marrow damage seventeen developed leukemia; this is an incidence higher than

Table 1

Erythroleukemia virus activity in irradiated and non irradiated chicks

Days between irradiation and virus inoculation	Radiation plus virus		Virus only	
	Number of dead versus number of inoculated	$\sum \frac{1}{t}/N$	Number of dead versus number of inoculated	$\sum \frac{1}{t}/N$
2	7/10	0.066	7/10	0.070
8	8/12	0.057	8/11	0.071
20	7/12	0.047	7/12	0.056
	22/34	0.056	22/33	0.065

slight granulopoietic activity and the other samples had mild erythropoietic activity.

Twelve days after irradiation The marrow in this group was regularly fatty and hypocellular, and necrosis was only slight compared with earlier groups. Hematopoietic activity was limited to the periphery where most samples had slight to moderate erythropoietic activity (Fig. 4). One of the four birds also exhibited moderate granulopoietic activity.

Twenty days after irradiation The marrow in this group was usually hyperplastic, with moderate to marked erythropoietic and granulopoietic activity. The fat content of the marrow compared with that of the abovementioned groups and the controls was reduced. One of the four chicks had changes that deviated considerably from the others. This chick had a hypoplastic fatty marrow with evidence of slight erythroid and myeloid cell proliferation (Fig. 5). No edema or cellular necrosis were seen in the marrow.

The bone marrow damage and regeneration were uniformly distributed. The marrow of both femora and tibiae was essentially similar in each chick. A biopsy sample of the femur marrow was considered to represent the radiation damage to the whole marrow in the following experiments on the combined effects of irradiation and erythroleukemia virus.

Combined treatment of chicks with radiation and erythroleukemia virus The combined treatment with radiation and erythroleukemia virus in the control chicks gave overall results similar to those in which treatment was with virus alone (Table 1).

Table 2

Correlation of erythroleukemia virus activity with the degree of radiation marrow damage (A) and incidence of erythroid regeneration (B)

	Number of dead versus number of inoculated	$\sum \frac{1}{i} / n$
A		
Irradiated chick with advanced marrow damage (3 and 4+)	4/13	0.025
Irradiated chicks with light marrow damage (1 and 2+)	17/21	0.092
B		
Irradiated chicks with histologic evidence of erythroid regeneration	17/25	0.062
Irradiated chicks without histologic evidence of erythroid regeneration	4/9	0.078
Non irradiated control chicks	22/33	0.063

The incidence of leukemia at corresponding ages was almost identical in the experimental groups and the control groups. The susceptibility of the chicks as calculated according to

$$\sum \frac{1}{i} / n$$

was identical in the experimental groups and the control groups at 2 days and 20 days after irradiation. At 8 days the control group had a slightly higher susceptibility.

The biopsies revealed that these experimental groups differed from the above mentioned groups by having greater intra group variations of radiation damage. Thus some of the chicks that were inoculated with virus 20 days after irradiation had persistent widespread cellular necrosis of the marrow or aplasia with marked fatty infiltration (Fig. 6). Placing the birds according to the presence of severe marrow damage and advanced hypocellularity into one group (3 and 4+) and those according to the presence of slight to moderate necrosis or hypocellularity into another (1 and 2+) irrespective of the time of virus-inoculation gave the figures recorded in Table 2.

The chicks with severe marrow damage histologically classified as 3 or 4+ had markedly reduced susceptibility for the virus and only four out of thirteen chicks developed leukemia. Of the twenty-one chicks with slight or moderate marrow damage seventeen developed leukemia; this is an incidence higher than

in the control chicks. The lower susceptibility correlated with severe marrow damage is also evident from the calculated activity values according to

$$\sum \frac{1}{t_i} / N$$

where both the latent periods and incidence influence the values. It is also obvious from Table 2 that erythroid regeneration in the radiation damaged marrow contributes to the susceptibility of the chicks to the virus. Chicks with evidence of erythroid regeneration in the marrow were much more susceptible than chicks without evidence of erythroid regeneration.

Histologic examination of the irradiated and virus-inoculated chicks, dying or killed in the terminal stage of erythroleukemia, revealed persistent bone marrow necrosis in four chicks, with only slight leukemic infiltration despite heavy leukemic infiltration in other organs (Figs 7 and 8).

Discussion

The results obtained clearly demonstrate that advanced cellular necrosis of the bone marrow produced by a single dose of irradiation inhibits the development of erythroleukemia (Table 2). The most likely cause of this inhibitory effect is that the target cells for the virus are damaged and reduced in number. The marrows with advanced necrosis contained very few viable cells scattered throughout its highly edematous marrow. There was a striking difference in susceptibility to the virus between this group and the one with only slight or moderate damage. The latter group had an increased susceptibility also in comparison with unirradiated control groups. This is interpreted as being due to rapid regeneration whereby the marrow will contain actively proliferating erythroid cells which are the target of the virus. The difference in susceptibility to the virus might thus be explained by the shortage or abundance of immature proliferating erythroid cells. This hypothesis was checked by grouping the experimental chicks according to histologically demonstrable erythroid proliferation in one group and absence of erythropoietic activity in another group (Table 2, group B). The erythropoietically active group was more susceptible to the virus than the inactive group. The activity values were not as high as in the group classified as having slight radiation damage. The difference is small, however, and largely due to longer latent periods in the group classified as presenting evidence of erythroid regeneration.

The total leukemia incidence is almost identical in the irradiated and the non irradiated groups, and only shorter latent periods increase the activity values in



Fig 7 Fat marrow containing scattered foci of leukemia cells in a chick dying of fulminant erythroleukemia following exposure to radiation 17 days previously. Hematoxylin-eosin $\times 350$.

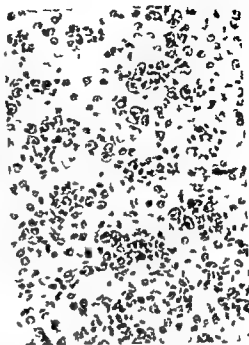


Fig 8 Liver from the same case as in fig 7. Heavy leukemic infiltration with sinusoids distended by leukemia cells. Hematoxylin-eosin $\times 350$.

the unirradiated group. It is thus obvious that the decrease in susceptibility dependent upon radiation damage is compensated for by the increased susceptibility of the chicks with only slight marrow damage.

The dose of virus administered has been the same in all the groups. The short latent periods from inoculation to death indicate that the virus preparations have been very active. No further attempts have been made in the present study to determine whether changing the virus dose would influence the response of the irradiated marrow.

The results obtained support the hypothesis that the pathogenic effect of this oncogenic virus is primarily dependent upon the presence of specific target cells. Whether the increased susceptibility reflects only the increased number of actively proliferating erythroid cells or whether irradiation has also caused a qualitative change in the cells cannot be settled by the results so far obtained. It is interesting to note that at the terminal stage of the leukemia only light

leukemic infiltration was present in the fatty or edematous marrow of some of the irradiated chicks, despite heavy infiltration in other organs. Radiation damage obviously reduced the capacity of the marrow not only to develop leukemia but also to support the growth of neoplastic cells.

Acknowledgement

The investigation was supported by grants from the Swedish Cancer Society and the Theresé and Johan Andersson's Foundation and by a grant to one of the authors (C H Chi) from the Swedish International Development Authority. The skilful assistance rendered by Miss Yvonne Kock and by Mr Ivar Jonsson of Radiumhemmet is gratefully acknowledged.

SUMMARY

Croups of chicks were inoculated with erythroleukemia virus 4, 8 and 20 days after exposure to 600 rad ^{60}Co radiation. Biopsy material from the femur marrow was obtained immediately prior to the virus inoculation. The incidence of leukemia and the latent periods to death of the chicks were recorded and a comparison is made between the groups of irradiated plus virus inoculated chicks and respectively only virus inoculated chicks. The results support the view that the pathogenic effect of the virus can be modified by varying the number of target cells and their differentiation.

ZUSAMMENFASSUNG

Cruppen von Küken wurden mit 600 rad ^{60}Co bestrahlt und 4, 8 und 20 Tage nach der Bestrahlung mit dem Erythroleukamievirus geimpft. Unmittelbar bevor der Impfung wurde Biopsiematerial aus dem Femurmark genommen. Die Untersuchungsergebnisse mit Hinsicht auf das Auftreten von Leukämie und die Latenzperioden bis zum Tode der Küken werden für die beiden Cruppen von bestrahlten und Virus injizierten Küken bzw. nur Virus injizierten Küken in Relation gestellt. Die Ergebnisse deuten darauf hin, dass der pathogene Effekt des Virus durch Veränderungen in der Anzahl von Target Zellen und in ihrem Differenzierungsgrade modifiziert werden kann.

RÉSUMÉ

Des groupes de poussins ont été inoculés avec le virus de l'érythroleucémie quatre, huit et vingt jours après avoir été exposés à une dose de 600 rad de ^{60}Co . Les poussins qui sont morts de leucémie ont été examinés histologiquement. Les auteurs ont comparé la fréquence de la leucémie et la période de latence jusqu'à la mort des poussins chez ceux qui avaient reçu l'irradiation et le virus et chez ceux qui n'avaient reçu que le virus. Les résultats de cette expérience viennent à l'appui de l'hypothèse que l'effet pathogène du virus peut être modifié au moyen de changements dans le nombre de cellules cibles et dans leur degré de différenciation.

REFERENCES

- HARAN GHERA N and NAPLAN H S Significance of thymus and marrow injury in urethane leukemogenesis *Cancer Res* 24 (1964) 1926
- NAPLAN H S On the natural history of the murine leukemias *Cancer Res* 27 (1967) 1325
- LAGERLOF B In vitro investigations of the virus induced fowl erythroleukemia I Long term cultivation of normal and leukemic bone marrow cells II The production of virus by cultured erythroleukemia cells and cultured normal cells exposed to the erythroleukemia virus in vitro *Acta path microbiol scand* 49 (1960) 344 and 361
- and SUNDELIN P Variations in the pathogenic effect of myeloid fowl leukemia virus *Acta path microbiol scand* 59 (1963) 129

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SUMMARY

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ZUSAMMENFASSUNG

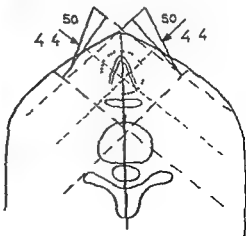
Gruppen von Küken wurden mit 600 rad ^{60}Co bestrahlt und 4, 8 und 20 Tage nach der Bestrahlung mit dem Erythroleukamievirus geimpft. Unmittelbar bevor der Einimpfung wurde Biopsiematerial aus dem Femurmark genommen. Die Untersuchungsergebnisse mit Hinsicht auf das Auftreten von Leukämie und die Latenzperioden bis zum Tode der Küken werden für die beiden Gruppen von bestrahlten und Virus injizierten Küken bzw. nur Virus injizierten Küken in Relation gestellt. Die Ergebnisse deuten darauf hin, dass der pathogene Effekt des Virus durch Veränderungen in der Anzahl von Target Zellen und in ihrem Differenzierungsgrade modifiziert werden kann.

RÉSUMÉ

Des groupes de poussins ont été inoculés avec le virus de l'érythroleucémie quatre, huit et vingt jours après avoir été exposés à une dose de 600 rad de ^{60}Co . Les poussins qui sont morts de leucémie ont été examinés histologiquement. Les auteurs ont comparé la fréquence de la leucémie et la période de latence jusqu'à la mort des poussins chez ceux qui avaient reçu l'irradiation et le virus et chez ceux qui n'avaient reçu que le virus. Les résultats de cette expérience viennent à l'appui de l'hypothèse que l'effet pathogène du virus peut être modifié au moyen de changements dans le nombre de cellules cibles et dans leur degré de différenciation.



Fig 1 Narrow beam exposures in one and the same film used for locating carcinoma of the pelvis and for pelvimetry. Contrast medium is seen in the lymph nodes



Figs 13 Field check in a case of laryngeal carcinoma (left) and position of fields (right)

CLINICAL APPLICATIONS OF A FIELD POSITIONING AND SIMULATING STAND

by

JOHN JOHANSSON, BENCT ROSENGREN and BENCT TJERNBERG

The field positioning and simulating stand described in a previous paper by JUNG, LARSSON, ROSENGREN et coll. has been applied clinically in connection with the planning of treatment with high energy radiations as well as for field checking.

Conventional roentgen stands are built to enable projections to be set up that provide the best diagnostic opportunities, while therapeutic stands are constructed with a view to achieving the optimal dosage distribution. The design of the simulator stand makes it possible to reproduce the angles used with therapeutic machines under identical conditions and with the correct focus-skin distance, herein lie the constructive peculiarities of simulators.

In *treatment planning* it is possible to localize, by means of a variety of projections, usually with the central ray horizontal or vertical, and to mark out on the patient's skin the positions of vertebrae and other parts of the skeleton, organs that can be filled with contrast medium, e.g. the bladder (for bladder tumours), and regions that at operation have been marked by indicators, usually in the thorax or abdomen.



Fig 1 Narrow beam exposures in one and the same film used for locating carcinoma of the pelvis and for pelvimetry. Contrast medium is seen in the lymph nodes.

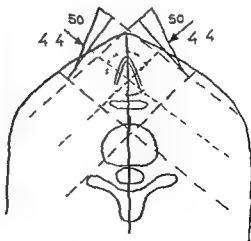


Fig 2 and 3 Field check in a case of laryngeal carcinoma (left) and position of fields (right)



Fig 4

Figs 4 and 5 Field check in a case of oesophageal carcinoma (left) and position of the fields in different planes (right)

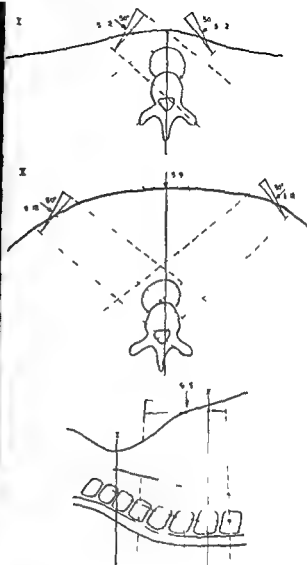


Fig 5

Positioning is possible also if the region to be treated cannot be rendered visible by any of the techniques just mentioned since in such cases the region to be irradiated can be marked out by guidance of its known relationships to various skeletal landmarks. Certain skeletal details in the pelvis may for example in gynaecologic treatment be employed as markers during the planning stage.

It is most important that organs or parts of organs that should not be exposed to unnecessary radiation can readily be located. A good example is the determina-



Fig 6



Fig 7

Figs 6 and 7 Field check in a case of embryonic tumour of the testis undergoing irradiation of the lumbar lymph nodes (left) and position of the field (above)

tion of the position of the spinal cord. When lymph nodes in the hilar regions of the kidneys are to be treated, it is possible to avoid irradiation of the kidneys themselves by localizing them by means of urography performed during the examination with the simulator.

Positioning so-called indication is commonly carried out by first obtaining a survey view of the general region and then stepping down to narrow slits so that in principle merely the central ray is used. By moving the patient sideways or vertically in the narrow beam the margins of the region to be irradiated may then be marked out on the patient and the measurements transferred directly to the dosage plan. If a roentgen film is placed under or beside the patient and several narrow beam exposures are made on the same film, measurements may be obtained directly from the roentgen image without consideration of enlargement factors. Such a method used for localizing carcinoma of the pelvis in women is illustrated in Fig 1.

Field checks are most important when small fields are employed and accurate positioning is essential, e.g. in cases of laryngeal carcinoma for which the vocal cord region must be in the middle of the region to be irradiated so that irradiation of the spinal cord is avoided. An example of this appears in Figs 2 and 3. Experience has shown that it may be difficult to position fields when the longitudinal axis of the tumour region forms an angle with the horizontal plane, e.g. in oesophageal carcinoma. The pendulum axis as well as the position of the collimator must then be angled. The field positioning and simulator stand makes this comparatively simple, a field check of this type is shown in Figs 4 and 5. It is also difficult to position the region to be treated so that the spinal cord is avoided in irradiation of the lumbar lymph nodes, e.g. in cases of embryonic tumours of the testes. A field check in such a case appears in Figs 6 and 7. Checking is usually made with an image intensifier and then, if desirable, the observations are documented on a roentgen film placed in the cassette holder on the image intensifier.

In conclusion it may be stated that the simulator has been found to be indispensable both for dose planning and field checking.

SUMMARY

The clinical applications of a field positioning and simulating stand are described.

ZUSAMMENFASSUNG

Die praktische Anwendbarkeit eines Bestrahlungssimulators für Feldlokalisierung wird besprochen.

RÉSUMÉ

Les auteurs décrivent les applications cliniques d'un stand de mise en place des champs et de simulation.

REFERENCES

- JUNG B, LARSSON B, ROSENCREN B et coll. A roentgen stand for field positioning in high energy radiotherapy. *Acta radiol Ther Phys Biol* 7 (1968) 282.

INTRACAVITARY THIOTEPA IN MALIGNANT PLEURAL AND PERITONEAL EFFUSIONS

by

A P ANDERSEN and H BRINCKER

A number of methods for controlling the exudation in serous cavities, in the palliative treatment of cases of effusions of malignant origin have been introduced during the past two decades. Resort had previously to be made to frequent paracenteses sometimes supplemented by roentgen irradiation to large thoracic or abdominal fields. Radiotherapy frequently caused severe side reactions and its effect was often poor. Hormonal therapy was only occasionally beneficial.

Intracavitary application of radioactive isotopes was introduced in 1945 by MÜLLER who used ^{65}Zn and later (1950) ^{198}Au . Numerous reports have since been published inter alios by DENNIS et coll (1956), HANSEN & HAUG (1960) and LAMBRECHTSEN & SELL (1961) on favourable results with ^{198}Au the exudation ceasing or being reduced in 50 to 70 per cent of the cases. However this treatment has the drawback of requiring specially trained staff which will be exposed to a certain amount of radiation even with the best apparatus. Furthermore it is rather costly and not suited for ambulatory use.

GLADIO & PERCESEPE (1958) employed prednisolone intrapleurally in a

Submitted for publication 11 December 1967

Table 1

Therapeutic results of intrapleural and intraperitoneal instillation of various cytostatics

Authors	Agent	Number of cases	Favourable effect	Side effects
BATMAN et coll	Thiotepa	24	16/24 66.7 %	
CROPIK & CUDMORI	Thiotepa	27	20/27 74.1 %	Bone marrow depression
GOODMAN et coll	KC 33	60	33/60 55.0 %	
WEISBERGER et coll	HN2	41	26/41 63.4 %	Bone marrow depression local pain
RIEVE & MYHRE	HN2	13	11/13 84.6 %	Nausea
SUHRLAND & WEISBERGER	5 fluorouracil	52	29/52 55.8 %	Bone marrow depression
CITTHORN et coll	Quinacrine	31	14/31 45.2 %	Fever local pain

Table 2

Distribution by primary tumour, sex and site of effusion

Primary tumour	Number of cases			Number of treated effusions		
	Males	Females	Total	Pleural cavity	Peritoneal cavity	Total
Breast cancer	0	16	16	14	2	16
Ovarian cancer	0	35	35	5	34	39
Cervical cancers (ovarian cancer excl.)	3	6	9	3	6	9
Gastrointestinal cancer	2	1	3	1	2	3
Cancer of the lung	3	5	8	8	0	8
Malignant lymphomas	3	3	6	8	0	8
Other cancers	6	3	9	3	6	9
Total	17	69	86	42	50	92

group of 20 cases with malignant pleural effusions. The treatment caused no complications and produced a positive result in 70 per cent of the cases.

Obliteration of the pleural cavity has also been employed in the treatment of malignant pleural effusions. HAUER et coll (1960) and STARKY (1964), for instance, used intrapleural talc poudrage, while JENSEN et coll (1963) performed pleurectomy. The results of these therapeutic methods appear to have been extremely satisfactory although it must have been unfortunate that such pro-

Table 3

Effect of intracavitary thiotepe in relation to primary tumour in the various groups

Primary tumour	Symbols for groups used in the assessment see pp 372-373				Total
	++ & +	(++) & (+)	#	?	
Breast cancer	1}	76 (47.2 %)	8	4	16
Ovarian cancer	6}		11	12	39
Cancer of the lung	1		1	0	8
Malignant lymphomas	2		1	2	8
Other cancers	2		1	7	21
Total	12		22	25	92
	54 (57.6 %)				

tients often in a poor general condition had to be exposed to an operative procedure

KARLOVSKY *et coll* (1948) reported that they had obtained regression of recurrent pleural effusion following the intracavitary instillation of nitrogen mustard (HN2) in a case of bronchogenic carcinoma. Since then, other alkylating cytostatics have been tried and have included in addition to HN2 AC-33 (N-hexamethylene N,N-diethylene thiophosphoramidate) and thiotepe (N,N,N-triethylene thiophosphoramidate). Other agents have also been administered e.g. the pyrimidine analogue 5-fluorouracil (SUNRLAND & WEISBERGER 1965) and the antimalarial quinacrine (GELLHORN *et coll* 1961).

The results of treatment with the mentioned substances in a varying series of malignant effusions are presented in Table 1. The results appear to be similar to those obtained with ¹⁹⁸Au. Direct comparison of the various substances and series is however hardly possible since the assessment criteria often differ and the number of unassessable cases varies.

Treatment with cytostatic agents has considerable advantages over the other therapeutic methods mentioned. Cytostatics are easy to administer, they are also relatively cheap and require no special apparatus or specially trained staff. The side effects are generally mild and usually restricted to bone marrow depression. However, HN2 may produce local pain and nausea, and quinacrine may also induce fever. These two substances should therefore be given only to inpatients while the others are well suited for the outpatients clinics.

Material and therapeutic procedure. The material comprises 86 cases treated during the period 1956-1967 and was made up of sixty-eight from the Radium

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Genital cancers (ovarian cancer excl)	3	6	9	3	6	9
Gastro-intestinal cancer	2	1	3	1	2	3
Cancer of the lung	3	5	8	8	0	8
Malignant lymphomas	3	3	6	8	0	8
Other cancers	6	3	9	3	6	9
Total	17	69	86	42	50	92

group of 20 cases with malignant pleural effusions. The treatment caused no complications and produced a positive result in 70 per cent of the cases.

Obliteration of the pleural cavity has also been employed in the treatment of malignant pleural effusions. HAUPT et coll (1960) and STARKEY (1964), for instance, used intrapleural talc poudrage, while JENSEN et coll (1963) performed pleurectomy. The results of these therapeutic methods appear to have been extremely satisfactory although it must have been unfortunate that such pa-

Table 5

Other simultaneous treatments in groups (+ +) and (+)

	Group (+ +)	Group (+)	Total
Relevant roentgen therapy	3		3
Hormone and/or castration therapy	4	3	7
Irritation of Au		2	2
Systemic cytotoxic therapy	4	2	6
Intracavitary thiotepa at first paracentesis	2	2	4
Total	13	9	22

been instituted less than 2 months prior to the thiotepa therapy or else thiotepa was administered at the very first paracentesis

0 indicates an unchanged frequency of punctures and/or fluid production

2 indicates unassessable cases due to (1) death within 2 months of the first administration of thiotepa (2) prophylactic treatment and (3) deficient data

Other simultaneous treatments consisted in (A) relevant radiotherapy (B) hormone therapy with or without castration and (C) systemic cytotoxic treatment

Results

The results of the treatment in relation to the primary tumour are given in Table 3. The majority of the cases of mammary carcinoma, pulmonary carcinoma and malignant lymphoma had pleural effusions while the others had mostly peritoneal effusions (cf Table 2).

In Table 4 the relationship between the therapeutic effect and the site of effusion is illustrated. The thirty-three unassessable cases were almost without exception in a wretched state and survived for less than two months after thiotepa therapy. Twenty-two received some other simultaneous treatment or else intracavitary thiotepa at the very first paracentesis. They have therefore been classified as (+ +) or (+). The numerical distribution of these groups is listed in Table 5.

The therapeutic results for the entire material as well as for pleural and peritoneal effusions separately are set out in Table 6 in relation to other materials treated with intracavitary application of alkylating agents. In these other materials unassessable cases do not appear to have been excluded and only GROTSBECK & CAPMORE (1962) give any detailed account of other concomitant treatment. If unassessable cases are excluded a favourable effect

Table 4

Effect of intracavitary thiotepea in relation to site of effusion

Effect*	Pleural effusions	Peritoneal effusions	Total
++	2	4	6
+	3	3	6
(++)	11	5	13
(+)	5	4	9
0	8	17	25
?	16	17	33
Total	42	50	92

* For explanation of symbols see pp 372—373

Centre in Aarhus and eighteen from the Radium Centre in Odense. The distribution, by primary tumour, sex, and site of effusion, is indicated in Table 2. The group of 35 cases with ovarian carcinoma includes eleven cases in which only the ascitic fluid had been examined histologically, but the clinical course had been typical of ovarian carcinoma. The number of treated effusions amounts to 92 since a few patients had effusions in two or three sites. Seventy-seven of the patients were in the age group 40 to 70 years, six being older and three younger. At the time when the analysis was closed (June 1st, 1967) seventy-three patients had died, while thirteen were alive and attending ambulatory control. No patient had been lost to follow-up.

The therapeutic procedure was as follows. After adequate paracentesis, 45 mg thiotepea dissolved in 10 ml water were instilled direct through the same needle. The dose was however sometimes 30 mg into the pleural and 60 mg into the peritoneal cavity. Two children received a small dose adapted to body weight.

Assessing the results, the following symbols were used:

++ No paracentesis for more than 4 months (regardless of subsequent intractable recurrence)

+ No paracentesis for from 2 to 4 months, or a double interval between the punctures

(Within groups ++ and + any simultaneous treatment was started more than 2 months before the thiotepea therapy, and the frequency of punctures prior to this treatment had been less than 2 months)

(++) & (+) Same criteria as above but other simultaneous treatment had

Table 7

Effect of intracavitary thiotepe in relation to nature of effusion

Effect	Haemorrhagic effusions	Serous effusions	Chylous effusions	Unknown	Total
++ & + (+-) & (+)	13	21			34
0	4	21			25
	13	18	1	1	33
Total	30	60	1	1	92

For explanation of symbols see pp 372-373

cases received two instillations. Only four cases had from 3 to 11 instillations, but all responded to the first or second treatment. Later instillations being given for recurrences, generally with good effect. Eleven of the twenty-five cases that failed to respond received from 3 to 6 instillations. A favourable effect, if any, may thus be expected at least after the second instillation. If a case has shown no response at that time, the chances of a response to thiotepe are slight.

Fifty-seven of the eighty-six cases exhibited adequate haematologic control during the treatment. Thirty-five developed mild to moderate leukopenia and/or thrombocytopenia of a transient nature, but none had signs of serious bone marrow depression. No relationship was found between a positive response and signs of bone marrow depression, which thus does not appear to be essential for a favourable therapeutic result.

As already mentioned, seventy-seven of the subjects were in the 40 to 70 year age group; no definite difference was observed in the therapeutic results in those who were in their forties, fifties, or sixties.

Among the unassessable cases, thirty of which survived for less than two months after the thiotepe therapy, there was a preponderance of histories of less than two months duration, while among those with a favourable response to the treatment the majority of histories exceeded a year. Most of the unassessable cases were not, however, at the time of the treatment in such a poor general condition that a rapidly fatal course could have been predicted. It was a characteristic finding that while only about a quarter of the cases in the groups of breast and ovarian carcinoma were unassessable, about half the number of those with growths in other sites were unassessable.

Out of the remaining cases twelve patients survived for from 2 to 4 months,

Table 6

Effect of intracavitary thiotepe compared with other materials treated with alkylating agents

Site of effusion	Effect**	Incl unassessable	Excl unassessable	Average of other materials treated with alkylating agents
Pleural + peritoneal	++ & +		12/37 (32.4 %)*	
	++ & + and (++) & (+)	34/92 (37.0 %)	34/59 (57.6 %)	106/165 (64.2 %) Ref 1 6 7 15 and 19
Pleural	++ & +		5/13 (38.5 %)*	
	++ & + and (++) & (+)	18/42 (42.9 %)	18/26 (69.2 %)	42/61 (68.9 %) Ref 1 7 and 19
Peritoneal	++ & +		7/24 (29.2 %)*	
	++ & + and (++) & (+)	16/50 (32.0 %)	16/33 (48.5 %)	20/31 (64.0 %) Ref 1 7 and 19

* Group (++) & (+) also excluded

** For explanation of symbols see pp 372—373

of the treatment was obtained in 57.6 % of the present cases. This corresponds to an average of 64.2 % in other materials. But if the unassessable cases are included, a favourable result was obtained in 37.0 % of the present cases. Furthermore, if the therapeutic results are accepted as definitely positive only in cases that received no other simultaneous treatment, there is a favourable result in only 32.4 % of the cases after exclusion of the unassessable cases and the cases receiving other simultaneous treatment. The corresponding values for pleural and peritoneal effusions respectively are evident from Table 6.

Table 7 indicates the relationship between the nature of the effusion and the therapeutic result. An equally large number of cases (21/21) with serous effusions responded favourably or not at all. It will be seen that with haemorrhagic effusions a favourable response was obtained in 13 out of 17 cases. These values indicate the possibility of a better therapeutic result in this condition.

We also investigated the relationship between the therapeutic result and the number of instillations. Twenty three of the thirty four cases that responded well to the treatment needed only one instillation of thiotepe, while seven

Similarly the results appear to be better in the treatment of pleural than of peritoneal effusions. This has already been pointed out by BATEMAN *et coll* (1955), GROESBECK & CUDMORE (1962), and SUHRLAND & WEISBERGER (1965).

Conclusion

Treatment of malignant effusions with intracavitary thioteпа is of indubitable value in quite a large proportion of cases. It is devoid of risk to the patients as well as to the staff and entails so little discomfort and so few side effects that its selection for the first therapeutic attempt appears reasonable. The treatment seems to be most effective in mammary or ovarian carcinoma of long duration and in cases of haemorrhagic effusions. Pleural effusions appear to react better than peritoneal effusions. If the case does not respond by a reduction in the effusion after two installations of thioteпа other methods should be tried.

Acknowledgement

The authors wish to thank P. Bjerre HANSEN and E. LAMBERGENSEN for the loan of the case sheets.

SUMMARY

Thioteпа injections into the pleural and peritoneal cavities were given in a series of 86 cases. The treatment had a favourable effect in 37 per cent and if unassessable cases are excluded in 57.6 per cent of the cases. The greatest chance of response had cases with mammary or ovarian carcinoma of long duration and cases with haemorrhagic effusions.

ZUSAMMENFASSUNG

Thioteпа Injektionen in die Pleurahöhle und die Peritonealhöhle wurden in 86 Fällen durchgeführt. Eine günstige Wirkung der Behandlung wurde in 37 Prozent der Fälle erzielt und wenn man zweifelhafte Fälle ausschliesst in 57.6 Prozent. Die beste Voraussetzung für einen guten Erfolg erbieten Fälle von andauernden Brust- und Ovarialkarzinomen und Fälle mit hämorrhagischen Ergüssen.

RÉSUMÉ

Une série de 86 malades ont été traités par injection de thioteпа dans les cavités pleurale et péritonéale. Ce traitement a eu un effet favorable dans 37 pour cent de l'ensemble des cas et si on élimine les cas impossibles à juger il a eu un effet favorable dans 57.6 pour cent des cas. Les meilleures chances d'effet favorable se trouvent dans les cancers du sein ou de l'ovaire de longue durée et dans les cas d'épanchement hémorragique.

eight for from 4 to 6 months, eighteen for from 6 to 12 months, while three survived for more than a year. Thirteen patients were still alive at the time when analysis was closed.

Fifteen cases received intracavitary treatment with ^{90}Y or ^{199}Au before or after intracavitary thiotepe therapy. A favourable effect of isotope therapy after thiotepe was noted in six out of eleven cases and in three out of four cases a similar effect of isotope therapy prior to thiotepe was observed. All the four cases that received thiotepe after isotope therapy belonged to the group of unassessable cases.

Discussion

Intracavitary application of cytostatics makes it possible to obtain direct contact with malignant cells and thus to obtain a higher concentration than in systemic treatment. THOM (1964) found for instance that in malignant effusions treated with intracavitary thiotepe increasing oedema of the tumour cells occurred within a few hours. After 24 hours, there were signs of necrobiotic changes, with loss of nucleoli, in most of the tumour cells.

Our results with thiotepe do not appear to be as satisfactory as those obtained by other workers with alkylating agents (Table 6). However, if the unassessable cases are excluded, and the influence of other simultaneous treatments is disregarded, they are on a level with previous results, although the authors cited do not seem to have excluded their unassessable cases. It is possible that our criteria of a positive therapeutic result have been stricter, since the data of assessment are not always accurately defined in other materials. It could also be that in the present series the doses of thiotepe were too low, or that too few instillations were employed. However, the doses were of such a magnitude that in 61 per cent of the controlled cases they induced mild bone marrow depression. A favourable response, if any, appears moreover to be obtained after at the most two instillations. As compared with other materials, the series also does not seem to contain a preponderance of cases with carcinoma in sites that usually fail to respond favourably to intracavitary cytotoxic therapy. In other words, the results suggest that the effect of intracavitary thiotepe in malignant effusions is not as good as previously assumed.

It is always difficult to evaluate the effect of other treatments given at the same time, but assuming they be of less importance compared with intracavitary thiotepe treatment, the results indicate the greatest effect in the groups of mammary and ovarian carcinoma (Table 3). This is in accordance with the findings of WEISBERGER *et coll.* (1955) using HN2, GOODMAN *et coll.* (1965) with KC 33, and BOYTE *et coll.* (1956) with ^{199}Au .

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Treatment of malignant effusions with intracavitary thiotepe is of indubitable value in quite a large proportion of cases. It is devoid of risk to the patients as well as to the staff and entails so little discomfort and so few side effects that its selection for the first therapeutic attempt appears reasonable. The treatment seems to be most effective in mammary or ovarian carcinoma of long duration, and in cases of haemorrhagic effusions. Pleural effusions appear to react better than peritoneal effusions. If the case does not respond by a reduction in the effusion after two instillations of thiotepe, other methods should be tried.

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INTERCOMPARISON OF ABSORBED DOSE IN COBALT 60 TELETHERAPY USING MAILED LiF DOSIMETERS

by

P. M. PFALZNER and S. MALO ALVAREZ

The International Atomic Energy Agency has long been aware of the need for improved dosimetric accuracy in the medical applications of radiation such as in teleradiotherapy. Of all radiotherapy centres in the world probably less than 50 % have ready access to standardizing dosimetry laboratories and even these laboratories at present provide only standards of radiation exposure (in roentgen) whereas the decisive quantity in radiotherapy is the absorbed dose (in rad) received by the tissues being irradiated.

In order to assist radiotherapy centres particularly in the developing countries with the determination of absorbed dose in ^{60}Co teletherapy the IAEA has set up a postal dose intercomparison service utilizing thermoluminescent LiF powder. Prior to putting this scheme into practice the intercomparison procedures were tested with the co-operation of 19 radiotherapy centres in 6 countries. The participating institutes are listed in Table 1.

This report gives a brief description of the procedures and of the results with out identifying the results with any particular institute.

Method. Each participant was provided with a plastic water tank in which the irradiation was to take place as well as with instructions for the experimental

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REFERENCES

- 1 BATFMAN J C MOULTON II and LARSEN N J Control of neoplastic effusion by phosphoramidate chemotherapy Arch intern Med 95 (1955), 713
- 2 BONTE I J, STORAASLI J P and WEISBERGER A S Comparative evaluation of radioactive colloidal gold and nitrogen mustard in the treatment of serous effusions of neoplastic origin Radiology 67 (1956) 63
- 3 CLAUDIO F and PERCISPE F Trattamento dei versamenti pleurici da neoplasie polmonari e pleuro polmonari con prednisolone per uso topico Rif med 72 (1958) 1095
- 4 DENNIS J M, WORKMAN J II and BAUER R E Radioactive colloidal gold in the control of malignant effusions Amer J Roentgenol 75 (1956) 1124
- 5 GELLHORN A ZALDINWEBER J, ULTMANN J and HIRSCHBERG E The use of atabrine (quinacrine) in the control of recurrent neoplastic effusions Dis Chest 39 (1961) 165
- 6 GOODMAN L E, BAKAL D, TSOU K C et coll Clinical experience with N hexamethylene NN diethylene thiophosphoramidate (K-C-33), a new agent for breast and ovarian carcinoma Cancer (Philad) 18 (1965) 307
- 7 GROESBECK H P and CUDWORTH J T P Intracavitary Thio-TFPA for malignant effusions Amer Surg 28 (1962) 90
- 8 HANSEN P B and HAUG A Treatment of pleural and peritoneal carcinomatous effusions with radioactive gold (1956—1959) Acta radiol 53 (1960) 321
- 9 HAUPT G J, CAMERON R C, TEMPLETON J Y and GIBSON J H Treatment of malignant pleural effusions by talc poudrage J Amer med Ass 172 (1960) 918
- 10 JENSEN R, CACLE J E, MILLOY F et coll Pleurectomy in the treatment of pleural effusion due to metastatic malignancy J thorac cardiovasc Surg 46 (1963) 322
- 11 KARNOFKY D A, ABELMANN W H, CRAVER L F and BURCHENAL J H The use of the nitrogen mustards in the palliative treatment of carcinoma Cancer (Philad) 1 (1948) 634
- 12 LAMBRITSEN E and SEIL A Palliative treatment of carcinomatous effusions in the pleural and peritoneal cavities with radioactive gold Acta radiol 56 (1961) 33
- 13 MÜLLER J H Über die Verwendung von künstlichen radioaktiven Isotopen zur Erzielung von lokalisierten biologischen Strahlenwirkungen Experientia 1 (1945) 199
- 14 — Weitere Entwicklung der Therapie von Peritonealcarcinosen bei Ovariecarcinom mit künstlicher Radioaktivität (Au¹⁹⁸) Gynaecologia 129 (1950) 289
- 15 REEVE T S and MYHILL J The role of radioactive isotopes and alkylating agents in the treatment of malignant effusions Med J Aust 2 (1962) 245
- 16 STARKEY G W B Recurrent malignant pleural effusions New Engl J Med 270 (1964) 436
- 17 SUJRLAND L G and WEISBERGER A S Intracavitary 5 fluorouracil in malignant effusions Arch intern Med 116 (1965) 431
- 18 THOM R Wirkungsunterschiede verschiedener Cytostatica bei serösen Ergüssen In H P Kuemmerle und P Preziosi Third International Congress of Chemotherapy Vol II, p 1220 Georg Thieme Verlag Stuttgart 1964
- 19 WEISBERGER A S, LEVINE B and STORAASLI J P Use of nitrogen mustard in treatment of serous effusions of neoplastic origin J Amer med Ass 159 (1955) 1704

Table 2
Intercomparison results

Institute number	Irradiated control capsules*			Test capsules		
	Individual values in per cent of overall mean			Extreme difference	R. m. s. deviation	Difference from mean
20	100.1	101.2	100.7	5.8	1.7	-2.0
21	101.5	100.0	99.5	5.0	1.8	-7.4
22	99.6	98.5	101.1	4.9	1.5	+2.1
24	99.7	98.2	100.1	5.9	2.4	-0.6
25	99.5	—	—	2.8	1.0	-8.3
26	98.7	101.0	100.7	7.0	2.0	-2.3
27	100.6	96.3	101.5	(11.6)	(3.8)	(+2.8)
27	—	—	—	8.6	2.4	+1.8
28	100.8	102.8	99.7	2.8	1.0	+1.0
29	98.9	99.6	100.5	(7.0)	(2.3)	(-8.4)
29	—	—	—	7.0	2.3	+0.4
30	100.4	97.9	99.6	9.9	1.0	+4.2
31	99.6	—	—	5.1	1.6	+3.5
31	101.1	98.1	—	4.4	1.0	+4.0
32	100.2	—	99.8	6.4	2.0	-1.1
33	99.8	101.8	99.4	5.6	1.7	-2.2
34	100.5	97.4	100.5	5.3	1.7	+1.1
35	100.8	—	—	9.9	3.2	0.0
36	97.4	—	—	5.2	1.5	-2.3
37	100.5	102.8	99.6	(7.2)	(2.3)	(+7.0)
37	—	—	—	7.2	2.3	+6.0
38	100.5	101.8	96.7	6.6	2.0	+1.5
A *	100.8	98.5	101.4	—	—	—
B	99.6	98.9	99.7	—	—	—
C	98.5	101.1	101.0	—	—	—

R. m. s. deviation = 1.4

Average r. m. s. deviation = 1.9

* The unirradiated controls in all cases gave readings which were less than 1% of those of the irradiated test capsules.

* A, B and C refer to irradiated control capsules kept in Vienna and read at different dates.

in stored luminescence due to unknown heating of the capsules while in transit and (3) to give an indication of the reproducibility of the procedure. The unirradiated control capsules served to detect any radiation which the set might have received while in transit.

Table 1

Participating institutes

Royal Adelaide Hospital, Adelaide	Australia
The Ontario Cancer Treatment and Research Foundation Ottawa	Canada
The Ontario Cancer Institute Toronto	Canada
Manitoba Cancer Treatment and Research Foundation Winnipeg	Canada
Institut Gustave Roussy Villejuif	France
Radiofysiska Institutionen Lund	Sweden
Regionsjukhuset Örebro	Sweden
Karolinska Sjukhuset Stockholm	Sweden
The General Infirmary Leeds	UK
The London Hospital and Research Laboratories London	UK
Westminster Hospital London	UK
Christie Hospital and Holt Radium Institute Manchester	UK
Regional Medical Physics Department Sheffield	UK
Royal Marsden Hospital Sutton Surrey	UK
Lovelace Clinic Albuquerque New Mexico	USA
Argonne Cancer Research Hospital Chicago Illinois	USA
M. D. Anderson Hospital and Tumor Institute Houston Texas	USA
Memorial Hospital New York N.Y.	USA
Temple University Hospital Philadelphia Pennsylvania	USA

procedure to be followed—The thermoluminescence readings of all capsules were carried out at the IAEA in Vienna using a commercial TLD read out instrument. Some of the precautions taken were (a) before each reading a radioactive phosphorescent light standard was introduced allowing corrections to be made for variations in instrumental sensitivity, (b) the photomultiplier voltage was kept constant at all times, (c) new heating planchets were used after each 15th heating cycle—At approximately monthly intervals, each one of the institutes received and returned one set of LiF capsules (up to a total of 5 sets), each set consisting of two control capsules and three test capsules. Each capsule contained some 150 mg of type 7 LiF powder (CAMERON *et al.* 1964). Each participant was instructed to irradiate the test capsules of each set, one at a time with a cobalt 60 beam of 10 cm×10 cm field size. The absorbed dose delivered to the capsules was to be 500 rad at a depth of 5 cm in water, the participant following his own method of dosimetry exactly as if treating a patient. One control capsule of each set was irradiated at the IAEA to a fixed dose before mailing, the other control capsule remaining unirradiated. Additional irradiated control capsules were retained in Vienna.

The irradiated control capsules served three purposes: (1) to obtain a decay curve of the stored luminescence as a function of time; (2) to detect any decrease

120 days later. A root mean square deviation of $\pm 1.4\%$ was found for the 36 control capsules.

The last three columns of Table 2 give the results for the test capsules. The fifth column gives the difference between the highest and lowest values as a percentage of the institute's mean, the next column gives the r.m.s. deviation from the institute's mean, and the last column gives the percentage difference between the mean for each institute and the overall mean.

Three institutes (Nos 27, 29 and 37) when returning the questionnaire but without any knowledge of the final results indicated that they wished to change the dose values they had previously reported. These institutes have been listed in duplicate with a prime indicating the revised calculations.

Discussion

In Tables 3 and 4, use is made of the data given in the participants' completed questionnaires. The four methods used by participants to calculate the absorbed dose in water are shown in Table 3. Two of these methods are based on in-air measurements and the two others on in-water measurements. For each of these there is again a choice between making the measurement at the actual position of the LiF capsule or at some other point.

It will be noted that in all of these methods, both the cap displacement factor C_D and the roentgen-to-rad factor f occur. The factor C_D is required to allow for changes in absorption and scatter whenever an ionization chamber calibrated to read exposure in an extended air medium is used for measurements in a different medium. The participants reported values of this factor for water are 0.985 for the Baldwin Farmer substandard chamber and the Victoreen 25 R and 100 R chambers, 0.975 for the Victrometer 250 R chamber, and 0.98 for the Baldwin Ioner.

The use of the factor C_D in methods 3 and 4 depends on the definition of TAR (and BSF). The definition given in ICRU Report 10d (1963) is in terms of ratios of absorbed dose and leads to values for both TAR and BSF slightly differing from the earlier ones (CUNNINGHAM et al. 1965, GUPTA et al. 1966). The use of these values requires a knowledge of the cap displacement factor C_L .—It appears possible to formulate a definition of TAR (and hence BSF) such that the factor C_D does not occur explicitly in the use of methods 3 and 4; this would be desirable for purposes of practical dosimetry.

Table 4 lists all participating institutes and gives the factors employed by them in calculating absorbed dose from measured exposure values. The differences from the overall mean (given in Table 2) are shown in column 2. It is instructive to see how much of this difference is due to differences in the factors used by

Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	$11F \times f \times C_D$
2	2	$11F_{0.5} \times \%DD \times f \times C_D$
3	6	$1E \times TAR \times f \times C_D$
4	5	$1F_{0.5} \times BSF \times \%DD \times f \times C_D$

(One participant did not give any information)

Legend

- $11F$ = exposure rate measured in water at position of LiF capsule
 $11F_{0.5}$ = exposure rate measured in water at (SSD + 0.5) cm
 $1E$ = exposure rate measured in air at position of LiF capsule
 $1E_{0.5}$ = exposure rate measured in air at (SSD + 0.5) cm
 $\%DD$ = central axis percent depth dose
 TAR = tissue air ratio
 BSF = backscatter factor
 f = roentgen to rad factor (rad/R)
 C_D = cap displacement factor
 $\%SSD$ = source to surface distance

Re method 2 One institute used this incorrectly the exposure rate was measured at the water surface and no correction factor was applied for the required change in distance to 11.5 cm below the surface

Re method 4 Two institutes used this incorrectly the exposure rate was measured in air at the SSD instead of at (SSD + 0.5) cm and no correction factor was applied

At the completion of the series, a questionnaire was sent to each participant concerning the data used by him in determining the administered dose

Results

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Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	${}_{18}E \times f \times C_D$
2	2	${}_{18}E_{0.5} \times \%DD \times f \times C_D$
3	■	$AE \times TAR \times f \times C_D$
4	5	$AE_{0.5} \times BSF \times \%DD \times f \times C_D$

(One participant did not give any information)

Legend

- ${}_{18}E$ = exposure rate measured in water at position of LiF capsule
 ${}_{18}E_{0.5}$ = exposure rate measured in water at (SSD + 0.5) cm
 AE = exposure rate measured in air at position of LiF capsule
 $AE_{0.5}$ = exposure rate measured in air at (SSD + 0.5) cm
 $\%DD$ = central axis percent depth dose
 TAR = tissue air ratio
 BSF = backscatter factor
 f = roentgen to rad factor (rad/R)
 C_D = cap displacement factor
 SSD = source to surface distance

Re method 2 One institute used this incorrectly the exposure rate was measured at the water surface and no correction factor was applied for the required change in distance to 0.5 cm below the surface

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Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	$15E \times f \times C_D$
2	1	$15E_{0.5} \times \%DD \times f \times C_D$
3	6	$AE \times TAR \times f \times C_D$
4	5	$AE_{0.5} \times BSF \times \%DD \times f \times C_D$

(One participant did not give any information)

Legend

$15E$ = exposure rate measured in water at position of LiF capsule

$15E_{0.5}$ = exposure rate measured in water at (SSD + 0.5) cm

AE = exposure rate measured in air at position of LiF capsule

$AE_{0.5}$ = exposure rate measured in air at (SSD + 0.5) cm

$\%DD$ = central axis percent depth dose

TAR = tissue air ratio

BSF = backscatter factor

f = roentgen to-rad factor (rad/R)

C_D = cap displacement factor

SSD = source to surface distance

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Table 4

Institute number	Difference from mean %	Recalculated* difference from mean %	Factors used by participants to	
			f rad/R	C_1^{**}
UK	20	-2.0	Not recalcd	0.944
	21	-7.4	-4.2 (-2.7)	—
	22	+2.1	+0.7	—
	24	-0.6	Not recalcd	0.944
	25	-8.3	(No information
	26	-2.3	Not recalcd	0.940
USA	27	+1.8	+1.4	—
	28	+1.0	+0.9 (+2.4)	—
	29	+0.4	-0.6 (+0.9)	—
	30	+4.2	+2.9 (+4.4)	—
	39	+3.5	+5.1 (+6.6)	—
			0.97	—
	31	+4.0	No change	0.965
	32	-1.1	Not recalcd	—
	33	-2.2	No change (-0.7)	0.97****
	34	+1.1	+2.3 (+3.8)	—
	35	0.0	No change	—
	36	-2.3	-4.2 (-2.7)	0.965
	37	+6.0	+5.9	0.96
	38	+1.5	Not recalcd	—

* For the calculations in this column values were taken to be $f(\text{water}) = 0.965$ BSF = 1.035
 $\%DD_{80} = 78.5$ TAR = 0.905 other factors were left unchanged

** $C_A = C_D \times f$ (see ref. 2)

participants to calculate absorbed doses. If we normalize all results by adopting uniform values for the f factor, BSF, % DD and TAR (as noted in Table 4) we can calculate the resulting percentage changes in the reported doses, and hence obtain revised values for the differences from the mean, as shown in column 3 of the table. For three institutes the missing inverse-square law factors were included in the recalculation. When account is taken of the need to include also the cap displacement factor C_D in the recalculation, the final revised values for the differences from the mean are as shown in brackets.

Table 4 (cont.)

calculate absorbed doses				
Field size 10 cm \times 10 cm			C_D	Method number
BSF	At 5 cm depth			
	DD _{55D}	TAR		
—	—	—	—	1
1 016 **	58 0 ₁₀ ^{***}	—	1 0	4
1 030	77 0 ₈₀ ^{***}	—	0 97 ₃	4
—	—	—	—	1
a. aifable	—	—	—	1
—	—	—	—	—
1 076	79 5 ₈₀	—	0 98 ₃	4
—	—	0 90 ₃	1 0	3
—	—	0 888	1 0	3
—	—	0 893	1 0	3
1 076	74 0 ₈₀	—	1 0	4
—	—	0 90 ₃	0 98	3
—	—	—	—	1
—	78 0 ₇₅	—	1 0	2
—	78 5 ₈₀	—	1 0	2
1 035	78 5 ₈₀	—	0 96 ₃	4
—	—	0 893	1 0	3
—	—	0 904	0 98 ₃	3
—	—	—	—	1

Report d as measured values for a 10 \times 8 cm field (a recalculation BSF was taken as 1 033)

* * Report d as measured values

Conclusions

The results of the intercomparison and the analysis permit certain conclusions to be drawn with respect to the differences between the participating institutes in both the determination of exposure and of absorbed dose

Table 2 (column 7) shows that maximum differences of up to 15 % in absorbed dose to patients may exist between some of the institutes. It is seen that four institutes account for the greatest deviations from the mean. However two of these reported corrections to their figures resulting in improved values and hence only three institutes deviate by more than 5 % from the overall mean.

The recalculated values of Table 4 (column 3), resulting from the adoption of common values for the factors and corrections for cap displacement and inverse square law (where necessary) in the calculation of absorbed dose from the participants exposure measurements, give an indication of the differences in exposure determination between the institutes (values for institutes using method 1 were not recalculated). The maximum differences (ignoring institute No. 25) are seen to be 9.3 %, i.e. the agreement as regards exposure is better than for absorbed dose but is nevertheless greater than one might expect for well established radiotherapy centres.

From the values of the recalculated percent differences, it can be deduced that the mean of these values is 1.1 % higher than the original overall mean. Taking this into account, it is found that only one institute shows a deviation of more than 5 %, and that the worst deviations are respectively +5.5 % and -3.8 % from the new overall mean. It is notable also that all of the six UK participants show a negative deviation from this new mean, and that of the 5 USA participants, four show positive deviations with only one having a small negative value.

The reliability of this particular method of intercomparison has proved to be adequate for present purposes as can be seen from Table 2. An indication of the value of this procedure can be obtained by comparing the results for institutes Nos. 27, 29 and 37 (as originally stated) with 27', 29', and 37' (as later corrected) in each of the three cases the change leads to improvement in the results.

The reliability of the system is indicated by the r.m.s. deviation of ± 1.4 % found for all the 56 irradiated control capsules taken together. The average of the r.m.s. deviations computed for each institute separately is ± 1.8 %—only slightly larger than that of the irradiated controls—indicating that on the whole the institutes are self consistent. A few institutes, however, do not show such good consistency: numbers 30 and 35, for example, both show extreme differences from the mean of 10 %.

The handling and mailing procedures of the capsules proved to be simple and nearly trouble free.

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SUMMARY

A procedure established by the IAEA for absorbed dose intercomparison in cobalt 60 teletherapy was tested with the cooperation of 19 radiotherapy centres in 6 countries. A series of dosimeter capsules containing LiF powder were distributed by mail and after irradiation to an absorbed dose of 500 rad at a depth of 5 cm in water were returned to the IAEA for read-out and evaluation. The results permit conclusions to be drawn concerning the reliability of the method of intercomparison and provide an indication of the consistency and range of disagreement existing in both absorbed-dose determination and exposure calibration. Root mean square deviations of respectively $\pm 14\%$ and $\pm 18\%$ were found for the readings of irradiated control capsules and test capsules. The maximum differences between institutes in absorbed dose and exposure determination were respectively 15% and 9%.

ZUSAMMENFASSUNG

Ein von der IAEA für Cobalt 60 Teletherapie ausgearbeitetes Verfahren zur Vergleichung von Energiedosis-Bestimmungen wurde in Zusammenarbeit mit 19 Radiotherapie Zentren in 6 Ländern untersucht. Zu diesem Zweck wurden eine Reihe von mit LiF Pulver gefüllten Dosimeterkapseln per Post an die 19 Institute versandt. Nach Bestrahlung mit einer Energiedosis von 500 rad in einer Tiefe von 5 cm Wasser wurden die Kapseln zur Auswertung an die IAEA retourniert. Schlussfolgerungen betreffs der Zuverlässigkeit dieser Vergleichsmethode als auch der Konsistenz bzw. der Streuung bei der Bestimmung von Energiedosis und Ionendosis werden gezogen. Die mittleren quadratischen Fehler bei der Ablesung der bestrahlten Kontrollkapseln bzw. Testkapseln betragen $\pm 14\%$ bzw. 18% . Die Maximaldifferenzen zwischen den von verschiedenen Instituten ermittelten Energiedosis- und Ionendosiswerten betragen 15% bzw. 9%.

RÉSUMÉ

Les auteurs ont mis à l'épreuve avec la coopération de 19 centres de radiothérapie de 6 pays un processus d'intercomparaison des doses absorbées en télécobaltthérapie processus établi par l'IAEA. Ils ont envoyé par la poste une série de capsules dosimétriques contenant de la poudre de LiF qui après irradiation à une dose absorbée de 500 rad à une profondeur de 5 cm dans l'eau ont été renvoyées à l'IAEA pour comptage. Les résultats permettent de tirer des conclusions concernant la fidélité de cette méthode d'intercomparaison et donnent une indication sur la constance et l'importance de la discordance quant à la détermination de la dose absorbée et de l'exposition. On a trouvé des écarts standard de respectivement $\pm 14\%$ et $\pm 18\%$ dans la lecture des capsules irradiées témoin et des capsules en expérimentation. Les différences maximales entre les divers instituts dans la détermination de la dose absorbée et de l'exposition ont été respectivement de 15% et de 9%.

REFERENCES

- 1 CAMERON J R, ZIMMERMAN D, KENNEY H et coll. Thermoluminescent radiation dosimetry utilizing LiF. *High Phys* 10 (1964) 25.
- 2 CODE OF PRACTICE FOR THE DOSIMETRY OF 2 TO 8 MV X ray and caesium 137 and cobalt-60 γ ray beams. The Hospital Physicists Association. *Phys Med Biol* 9 (1964) 457.

The recalculated values of Table 4 (column 3), resulting from the adoption of common values for the factors and corrections for cap displacement and inverse square law (where necessary) in the calculation of absorbed dose from the participants' exposure measurements, give an indication of the differences in exposure determination between the institutes (values for institutes using method 1 were not recalculated). The maximum differences (ignoring institute No. 25) are seen to be 9.3 %, i.e. the agreement as regards exposure is better than for absorbed dose but is nevertheless greater than one might expect for well established radiotherapy centres.

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ETUDE DE LA REPARTITION DES DOSES AUTOUR DE SOURCES PONCTUELLES ALIGNEES

Application en curietherapie gynecologique

par

A. DUTREIX et A. WAMBERSIE

Le remplacement progressif du radium par d'autres radioéléments a permis de renover les techniques d'application des sources radioactives et notamment de développer les méthodes de préparation inactive.

Simultanément et pour faciliter l'utilisation de ces techniques, on a mis au point des sources de forme et de dimensions très différentes. Ainsi certains auteurs (CARDIS 1968, C. E. A. 1966) proposent des sources de césium 137 sous formes de petites sphères ou de grains qui peuvent être assimilés à des points et que nous appellerons par convention 'sources ponctuelles'.

Les radiothérapeutes avant d'utiliser ces sources dans des applications pour lesquelles ils ont une grande expérience du radium désirent savoir à quelles modifications ils peuvent s'attendre dans la répartition des doses. Ceci est particulièrement vrai dans le cas des applications gynécologiques pour lesquelles les techniques utilisant les tubes de radium sont bien codifiées et donnent d'excellents résultats cliniques.

Nous avons entrepris l'étude de la répartition des doses dans ce cas mais la plupart de nos conclusions sont valables pour d'autres applications.

- 3 CLINICAL DOSIMETRY ICRU Report 10d (1962) NBS Handbook No 87 Nat Bur Standards Washington D C 1963
- 4 CUNNINGHAM J R, GUPTA S K and JOHNS H E An examination of the definition and magnitude of back scatter factor for cobalt 60 gamma rays (letter) Brit J Radiol 38 (1965), 637
- 5 GUPTA S K and CUNNINGHAM J R Measurement of tissue air ratios and scatter functions for large field sizes for cobalt 60 gamma radiation Brit J Radiol 39 (1966), 7

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Soumis à la Rédaction 13 Mai 1968

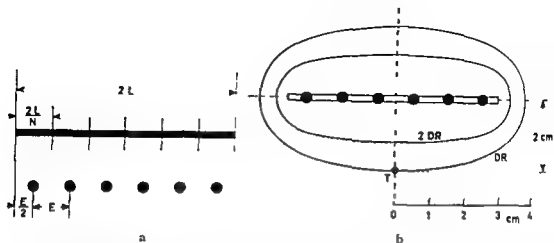


Fig. 1. Comparaison de sources ponctuelles alignées et d'une source rectiligne continue a) Disposition des sources ponctuelles équivalente à la source continue b) La dose de référence DR est définie au point T

Le calcul de la dose par les méthodes manuelles est extrêmement long et fastidieux et rend difficile toute étude systématique mais nous disposons pour ce travail d'un programme de calcul sur ordinateur (DUTREIX 1967) (Nous tenons à remercier le Centre de Calcul de l'Université de Louvain qui a fort obligeamment mis à notre disposition son calculateur (IBM 360—40) pour cette étude)

Dans une première partie, nous avons recherché la disposition des sources ponctuelles qui permet d'obtenir une répartition des doses aussi semblable que possible à celle correspondant à une source continue, cela pour répondre à la demande de certains curiethérapeutes.

Nous avons toutefois négligé pour cette comparaison l'autoabsorption dans la source continue, en considérant que la diminution de dose qu'elle entraîne à l'extrémité des sources n'est jamais souhaitable et qu'il serait donc illogique de chercher à la reproduire avec un autre dispositif.

Dans une deuxième partie nous avons cherché à établir des règles simples permettant de calculer la valeur de la dose en un point de référence et de prévoir les dimensions des isodoses en fonction du nombre de sources et de leur disposition.

Nous avons enfin étudié l'influence sur la forme des courbes isodoses d'un espacement irrégulier des sources.

I. Equivalence entre une source rectiligne continue et des sources ponctuelles

Il est évident que la répartition de la dose autour de sources ponctuelles alignées est d'autant plus semblable à celle autour d'une source continue

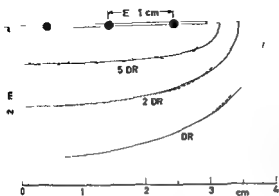


Fig 2 Distribution comparée des doses autour d'une source rectiligne continue de 6 cm de longueur radioactive et de 6 sources ponctuelles alignées espacées de 1 cm

que l'espacement entre les sources est plus faible (c'est à-dire le nombre de sources ponctuelles plus élevé) et que la distance à l'axe de ces sources est plus grande

Considérons (Fig 1) une source radioactive rectiligne continue de longueur active $2L$ cm et d'activité Q mCi que l'on décompose en N éléments égaux de longueurs $2L/N$. On peut remplacer chacun de ces N éléments par une source ponctuelle placée en son centre et d'activité Q/N mCi. Les N sources ponctuelles sont ainsi régulièrement réparties et l'espacement E entre deux sources est égal à $2L/N$.

Nous avons fait varier cet espacement entre les sources de 0,5 à 2 cm. Pour des espacements inférieurs à 0,5 cm, il est difficile de mettre en évidence des différences de répartition des doses même à quelques millimètres de l'axe des sources. Pour des espacements supérieurs à 2 cm, les variations de doses même à grande distance de l'axe deviennent trop importantes.

Pour inclure largement dans cette étude tous les types de sondes utilisés en gynécologie, nous avons délibérément fait varier les longueurs actives au-delà des limites usuelles et le calcul a été effectué pour des sources de longueur active variant de 4 à 12 cm.

Toutes les doses ont été estimées en fonction de la dose DR en un point de référence. Ce point de référence T est situé dans le plan perpendiculaire à l'axe de la source en son centre et à 2 cm de cet axe.

Le volume traité est le volume de tissu limité par l'isodose dont la valeur est égale à celle de la dose DR au point T .

Le volume de surdosage (2 DR) est le volume de tissu limité par l'isodose dont la valeur est égale à 2 fois celle de la dose DR au point T . De même on peut également définir des volumes de surdosage 3 DR , 4 DR etc.

Par convention on appelle

Longueur d'un volume, la dimension de ce volume mesurée dans la direction de l'axe de la sonde,

Rayon de ce volume, le rayon de l'isodose circulaire mesurée dans un plan perpendiculaire à l'axe de la sonde à une distance définie du centre de la sonde

L'analyse des résultats des calculs effectués pour les différentes longueurs actives et pour les différents espacements entre les sources nous a permis de comparer de façon précise les volumes précédemment définis et d'en tirer les conclusions suivantes (Fig. 2)

1 Volume traité

A Rayon Dans tous les cas envisagés dans cette étude, source continue ou sources ponctuelles, on peut admettre que le rayon du volume traité décroît régulièrement quand on se déplace du centre de la sonde vers une extrémité.

Le calcul montre que le rayon de ce volume à une distance définie du centre est indépendant de l'espacement entre les sources, tant que cet espacement est inférieur à 2 cm, il est égal au rayon du volume correspondant à une source continue.

Le rayon du volume traité dépend très peu de la longueur de la source au centre de la source, il est égal à 2 cm par définition, à une distance $L/2$ du centre, il est égal à 1,9 cm, à une distance $3L/4$ du centre, il est égal à 1,8 cm pour une source de 4 cm de longueur et à 1,7 cm pour une sonde de 12 cm.

Quand on passe d'une source continue de 12 cm de longueur à 6 sources ponctuelles espacées de 2 cm, la diminution du rayon n'est que de 1 mm même à 6 cm du centre, c'est à dire au niveau de l'extrémité de la partie active de la source continue.

B Longueur La longueur du volume traité est légèrement plus petite lorsque l'on passe d'une source continue à des sources ponctuelles. Elle diminue lorsque le nombre de sources diminue. La variation maximale observée est de 5 mm lorsque l'on passe d'une source continue de 12 cm à 6 sources espacées de 2 cm.

2 Volume surdose

A Rayon Lorsque l'on considère des isodoses plus proches de la sonde (de valeurs 2 DR, 3 DR, 4 DR) la forme de ces courbes peut être assez différente dans le cas d'une source continue et dans le cas de sources ponctuelles.

En effet pour une source continue le rayon du volume surdose décroît constamment du centre vers les extrémités alors que pour des sources ponctuelles il passe par une série de maximums et de minimums qui sont d'autant plus accentuées que la valeur de l'isodose est plus grande et que les sources sont plus espacées.

Dans le cas de l'isodose 2 DR, l'amplitude de la variation du rayon du volume surdosé est pratiquement indépendante de l'espacement entre les sources.

Ainsi pour une source continue de 12 cm de long le rayon décroît de 11 mm à 10 mm lorsque l'on s'éloigne du centre à 0,75 L dans le cas de 6 sources espacées de 2 cm la variation correspondante du rayon est de 12 à 9 mm.

De même si l'on compare une source continue de 4 cm et 3 sources espacées de 1,33 cm le rayon varie de 13 à 11 mm dans les deux cas.

B Longueur Les variations de la longueur du volume surdose sont très semblables à celles observées pour la longueur du volume traité.

On peut en déduire que malgré les variations de la forme du volume surdose en fonction du nombre de sources, le volume de tissus surdose est pratiquement constant il a même tendance à décroître légèrement lorsque le nombre de sources diminue.

Des conclusions semblables pourraient être tirées pour le volume surdose 3 DR.

3 Dose au contact de la sonde

La dose au contact de la sonde a été étudiée pour des diamètres de sonde de 4 mm 6 mm et 8,5 mm et pour des longueurs de 4 à 12 cm.

Cette dose qui est toujours très élevée du fait de la faible distance de la source est uniforme tout le long de la sonde dans le cas d'une source continue mais présente des maximums et des minimums très accentués dans le cas de sources ponctuelles.

Cependant la dose minimale ne doit pas être trop faible pour éviter un sous-dosage des tissus et la dose maximale ne doit pas être délivrée à un volume trop important à cause des risques de nécrose.

La dose minimale au contact diminue au contact de la sonde évidemment lorsque le diamètre de la sonde augmente mais même pour une sonde de 8,5 mm de diamètre quelle que soit sa longueur et le nombre de sources ponctuelles la dose minimale est au moins égale à 3 fois la dose de référence au point T.

Tableau I
Dimensions du volume traité

Nombre de sources	Espacement	Volume traité	
		Longueur ¹ calculée	Longueur réelle
4	1	5.5	5.88
4	2	9	9.06
5	0.8	5.6	5.9
5	1	6.5	6.7
5	1.6	9.2	9.22
5	2	11	10.96
6	1	7.5	7.58
6	1.33	9.33	9.32
6	2	13	12.96
8	0.5	5.75	5.98
8	1	9.5	9.46
8	1.5	13.25	13.12
8	2	17	16.84
10	0.8	9.6	9.54
10	1.2	13.4	13.22

¹ Par la formule empirique (1)

Ainsi, si on délivre 5 000 rad en T , la dose à la paroi de la sonde est au minimum égale à 15 000 rad et aucun sous dosage n'est à craindre.

La dose maximale au contact de la sonde est déterminée d'ailleurs par le diamètre de celle-ci que par le nombre de sources. Ainsi pour une source continue de 6 cm, et pour une dose de 5 000 rad en T , la dose au contact de la sonde passe de 34 000 rad pour une sonde de 8,5 mm de diamètre à 71 000 rad pour une sonde de 4 mm de diamètre. Si on remplace la source continue par quatre sources espacées de 1,5 cm, la dose maximale atteint 49 000 rad pour un diamètre de 8,5 mm et 174 000 rad pour un diamètre de 4 mm.

A partir du moment où la limite de tolérance des tissus est dépassée la valeur de la dose a moins d'importance que la masse de tissus à laquelle cette dose est délivrée. Or, nous venons de voir que les volumes de tissus surdosés étaient très semblables pour les sources continues ou ponctuelles.

Tableau 2

Doses en rad/jour à 2 cm de sources de césium ponctuelles alignées

n	Espacement cm						
		0.5	0.8	1	1.2	1.5	2
1		190.8					
2		381.6	378.7	369.7	361.9	357.8	337.2
3		572.4	554.4	573.7	500.0	475.0	438.0
4		763.2	715.9	652.3	613.0	564.9	511.1
5		954.0	869.0	765.3	698.4	638.2	555.1
6		1144.8	999.0	843.8	764.3	681.5	589.1
7		1335.6	1107.4	914.3	814.8	770.2	616.0
8		1526.4	1209.7	972.4	853.6	750.7	633.4
10		1908	1378.7	1067	910.6	800.2	663.7
12		2290	1513.2	1124.9	950.6	824.4	
14		3053	1697.8	1207.8	1007.0	860.8	
20		3816	1820.9	1258.1	1038.7		

4 Conclusion

Le remplacement des sources continues par des sources ponctuelles n entraîne pas de variations importantes dans la repartition des doses à condition que l'espacement entre les sources soit inférieur à 2 cm.

Ce sont donc des considérations techniques et pratiques qui devront dicter au radiothérapeute le choix du nombre de sources à utiliser.

II Choix du nombre de sources ponctuelles, de leur repartition et de leur activité

Le radiothérapeute qui desire utiliser des sources ponctuelles doit prévoir les dimensions du volume traité et calculer le temps d'application en fonction du nombre de sources utilisées et de leurs activités.

1 Dimensions du volume traité

Comme nous l'avons vu le rayon du volume traité est par définition égal à 2 cm.

La longueur de ce volume l (en cm) peut être calculée à partir d'une formule empirique

$$l = (N - 1) E + \frac{E}{2} + 2 \quad (1)$$

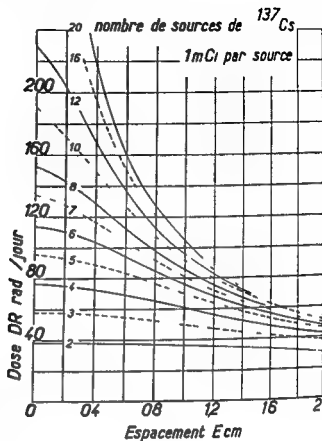


Fig 3 Variation de la dose de référence DR au point T en fonction du nombre N de sources et de leur espacement

ou E est l'espacement entre 2 sources en cm, c'est à dire que la distance s entre une source extreme et l'isodose DR est égale à $1 \text{ cm} + E/4$. L'erreur faite sur cette distance en utilisant cette formule empirique est inférieure à 2 mm comme le montre le Tableau 1

2 Calcul de la dose DR

La dose de reference DR delivree à 2 cm de l'axe de la sonde dans un plan perpendiculaire en son centre est proportionnelle à l'activité des sources et au temps d'application, elle n'est pas une fonction simple du nombre de sources et de leur espacement. C'est pourquoi nous avons construit une abaque permettant d'évaluer DR en rad/jour pour des sources de 1 mCi (Fig 3 et Tableau 2)

A partir de là, la dose totale DA delivrée au point de reference T au cours d'une application se calcule par la formule $DA = DR \cdot Q \cdot t$ ou Q est l'activité de chaque source en mCi et t le temps d'application en jours

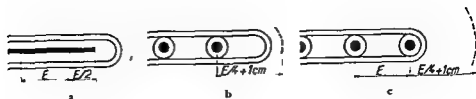


Fig 4 Choix de la disposition des sources dans une sonde intra utérine de longueur donnée
 a) La partie active de la source continue de radium n'atteint pas l'extrémité de la sonde la courbe pointillée représente l'extrémité de l'isodose DR b) Une distribution des doses analogue est obtenue en plaçant les sources ponctuelles suivant le schéma défini fig 1 c) La longueur du volume traité peut être augmentée en plaçant une source ponctuelle à l'extrémité de la sonde

3 Choix du nombre de sources et de leur espacement

La longueur S de la sonde est déterminée par la configuration anatomique de la malade mais le radiothérapeute a le choix du nombre de sources et de leur disposition

A Si l'on désire reproduire le plus exactement possible le schéma d'irradiation obtenu avec une source continue de radium de longueur active $2L$ et d'activité Q_{Ra} le nombre N de sources ponctuelles de césium leur espacement E et leurs activités individuelles Q_c sont liées par les relations

$$N E = 2L \quad N \Gamma_c Q_c = \Gamma_{Ra} Q_{Ra}$$

$$\text{d'où } Q_c = 2.5 Q_{Ra}/N$$

Γ_c et Γ_{Ra} sont les constantes spécifiques d'exposition du césium et du radium

$$\Gamma = 3.3 \text{ R cm}^2/\text{mCi h}$$

$$\Gamma_{Ra} = 8.25 \text{ R cm}^2/\text{mCi h} \text{ pour une filtration de } 0.5 \text{ mm de Pt}$$

Ainsi pour remplacer une source de radium de 30 mCi et de longueur active de 6 cm on peut utiliser 6 sources espacées de 1 cm (Fig 4) les sources ponctuelles extrêmes étant situées à 5 mm des extrémités de la zone active de la source continue. La longueur du volume traité est égale à $5 \times 1 + 2 + 0.5 = 7.5 \text{ cm}$

L'activité de chaque source de césium devrait être égale à $(2.5 \times 30)/6 = 12.5 \text{ mCi}$ pour que les temps d'application soient identiques et la dose DR à 2 cm serait égale à $6.5 \times 12.5 \text{ rad/jour} = 956 \text{ rad/jour}$

B Le radiothérapeute peut souhaiter profiter de la souplesse d'utilisation des sources ponctuelles pour irradier un volume un peu plus long

Il peut dans ce cas placer une source ponctuelle à chaque extrémité de la sonde la longueur de la sonde est $S \text{ cm}$ et si l'on dispose N sources ponctuelles régulièrement espacées de $E \text{ cm}$ on a $(N - 1) E = S$

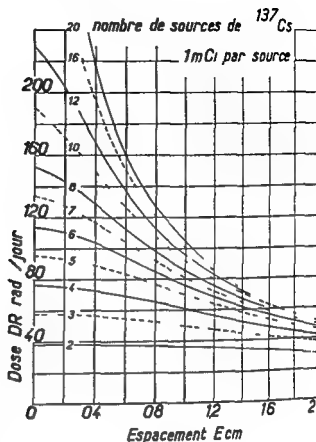


Fig 3 Variation de la dose de référence DR au point T en fonction du nombre N de sources et de leur espacement

ou E est l'espacement entre 2 sources en cm, c'est à dire que la distance s entre une source extrême et l'isodose DR est égale à $1 \text{ cm} + E/4$. L'erreur faite sur cette distance en utilisant cette formule empirique est inférieure à 2 mm comme le montre le Tableau 1

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A partir de là, la dose totale DA délivrée au point de référence T au cours d'une application se calcule par la formule $DA = DR \cdot Q \cdot t$, où Q est l'activité de chaque source en mCi et t le temps d'application en jours

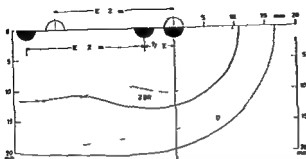


Fig 5 Influence sur le forme des isodoses de l'espacement entre les deux sources extrêmes Deux dispositions des sources ont comparées un espacement régulier (demi-cercles blancs et isodoses en pointillé) et un espacement réduit entre les deux sources extrêmes (demi-cercles noirs et isodoses en trait continu). On a fait coïncider les axes des sondes et les sources extrêmes. La réduction de l'espacement entre les sources extrêmes a pour effet d'augmenter le rayon du volume traité au niveau de l'extrémité de la sonde à nu que la distance s entre la source extrême et l'isodose DR.

2 Longueur du volume traité

Nous avons étudié les variations de la distance s entre la source la plus externe et la limite du volume traité (plus précisément le point d'intersection entre l'axe de la sonde et l'isodose DR).

Pour $E = 2$ cm et quand E_d passe de E à $E/4$ s augmente de 1 mm pour $\lambda = 4$ et 5 (s passe de 15 à 16 mm) et augmente de 3 mm pour $\lambda = 7$ et 8 (s passe de 14 à 17 mm).

Pour $E = 1$ cm et dans les mêmes conditions s augmente de 2 mm pour $\lambda = 4$ à 8.

Conclusion

L'adoption d'un espacement non uniforme des sources ponctuelles et en particulier une réduction de E_d ne modifie pas de manière importante la forme du volume traité dans les limites des dispositions envisagées. Le rayon du volume traité au niveau de l'extrémité de la sonde et la distance s peuvent être augmentées de quelques millimètres (Fig 5).

Toutefois lorsqu'on adopte un espacement non uniforme des sources le calcul de la dose de référence au point T ne peut pas être effectué à partir de Fig 3 ou du Tableau 2, il est indispensable de faire le calcul précis correspondant à chaque cas particulier.

Ainsi pour une sonde de longueur 6,5 cm, on peut placer 6 sources espacées de 1,3 cm, la longueur du volume traité est égale à $5 \times 1,3 + 2 + 0,65 = 9,15$ cm au lieu de 7,5 cm précédemment. Si on utilise les mêmes sources de 12,5 mCi, la dose à 2 cm est $652 \times 12,5 = 815$ rad/jour.

III. Espacement non uniforme des sources ponctuelles

Compte tenu de la plus grande souplesse dont on dispose avec les sources ponctuelles, on serait tenté d'essayer d'améliorer la forme du volume traité et en particulier d'augmenter son rayon au niveau des extrémités de la sonde et d'allonger la distance entre l'extrémité de la sonde et la limite du volume traité.

Ceci peut se réaliser en concentrant aux extrémités de la sonde une proportion plus grande de radioactivité. L'utilisation de sources d'activités différentes nous paraît peu recommandable en raison du risque possible de confusion entre les sources. Par contre, on peut songer à réduire l'espacement (E_d) entre la dernière et l'avant dernière source, ce qui ne doit pas poser de problèmes pratiques majeurs.

Nous avons étudié de manière systématique l'influence sur la forme du volume traité de la réduction de E_d à une valeur égale à $1/2$, $1/3$ et $1/4$ de l'espacement moyen E . Compte tenu des dimensions des sources que l'on peut être amené à utiliser, il nous paraît difficile de réduire E_d à une valeur inférieure à $E/4$.

1. Le rayon du volume traité

Nous avons étudié les variations du rayon du volume traité à la distance $0,75 L$ du centre de la source et à l'extrémité de celle-ci.

A. Variation du rayon à $0,75 L$. Quand on réduit E_d de E à $E/4$ et pour $E = 2$ cm, le rayon du volume traité augmente de 2 mm. Il passe de 18 à 20 mm pour $N = 4$ et 5 et de 19 à 21 mm pour $N = 8$.

Pour $E = 1$ cm et dans les mêmes conditions, le rayon du volume traité augmente de 1 mm, il passe de 18 à 19 mm.

B. Variation du rayon à l'extrémité de la sonde. Quand on réduit E_d de E à $E/4$ et pour $E = 2$ cm, le rayon du volume traité augmente de 2 mm pour $N = 4$ et 5 (il passe de 17 à 19 mm) et augmente de 4 mm pour $N = 6$ et 8 (il passe de 16 à 20 mm).

Pour $E = 1$ cm et dans les mêmes conditions, le rayon augmente de 2 mm.

DETERMINATION OF TUMOUR DOSE BY TRANSMISSION MEASUREMENTS IN ROENTGEN ROTATION TREATMENT OF THE OESOPHAGUS

by

ULLA BRITA NORDBERG

Determination of the tumour dose in conventional roentgen irradiation is very uncertain because of tissue inhomogeneity especially in the region of the thorax. This inhomogeneity is due essentially to the presence of lung tissue the density of which varies from patient to patient as well as within the same patient.

Attempts to measure depth doses in lung tissue have been made several times by FAILLA (1921), WEATHERWAX & ROBB (1930), QUIMBY *et coll.* (1934), NATHAN & NAIDOFF (1952) and DAHL & VIKTERLOF (1955) and others. The conditions under which the measurements were made have been very different however and so the results show no great agreement. NELMAN & WACHSMAN (1942) introduced a method for the calculation of the target dose in rotation treatment based on the measurement of transmission in principle on the conception of tissue air ratio (TAR). ROBBINS & MESZAROS (1954) determined the TAR value of homogeneous media of different shapes and sizes by phantom measurements for 250 kV roentgen rotation irradiation. LIDEN (1948) described dose determination directly in the oesophagus; this method has been employed

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RÉSUMÉ

Pour les applications gynécologiques (sondes intrautérines) le remplacement des sources continues par des sources ponctuelles ne modifie pas de manière importante la distribution des doses à condition d'adopter entre les sources un espacement qui ne soit pas supérieur à 2 cm. Ceci concerne tant la forme et les dimensions du volume traité que celles des volumes surdosés. Des tableaux et des graphiques sont proposés permettant le calcul rapide de la dose de référence et des dimensions du volume traité pour des sources ponctuelles régulièrement espacées. La diminution de l'espacement entre les sources extrêmes ne modifie pas de manière importante la forme du volume traité mais nécessite un calcul particulier des doses.

SUMMARY

The dose distribution in gynecologic treatments (intrauterine applicators) will not be much influenced by the substitution of point sources for continuous sources on condition that the distance between the sources is kept below 2 cm. This applies for the shape and dimensions of the treatment volume as well as of volumes receiving overdoses. Tables and diagrams are presented for a rapid determination of the reference dose and the dimensions of the treatment volume when using point sources regularly interspaced. A reduction of the distance between the extreme sources leads to no important modification of the treatment volume but necessitates a separate dose calculation.

ZUSAMMENFASSUNG

Die Dosisverteilung bei gynäkologischer Radiotherapie (intrauterine Sonde) wird bei der Substitution kontinuierlicher Strahlungsquellen gegen Punktquellen nicht viel beeinflusst, wenn man die Abstände zwischen den Strahlungsquellen unter 2 cm hält. Dies ist sowohl für die Form und die Dimensionen des behandelten Volumens wie für das überdosierte Volumen geltend. Tabelle und Diagramme werden für die schnelle Berechnung der Referenzdosis und die Dimensionen des Behandlungsvolumens bei Anwendung von Punktquellen, die in gleichen Abständen platziert sind, vorgeschlagen. Bei einer Reduktion des Abstandes zwischen den extremen Quellen wird das Behandlungsvolumen nicht viel beeinflusst, aber eine besondere Dosisberechnung ist erforderlich.

BIBLIOGRAPHIE

- CARDIS R. Sources de ^{137}Cs sphériques et de volume réduit d'activité nominale unique pour la curiethérapie gynécologique. *Ann. Radiol.* 11 (1968) 93.
 C. E. A. Catalogue des Radioéléments artificiels p. 15. C. F. A. Gif-sur-Yvette, France, 1966.
 DUTREIX A. Utilisation d'un ordinateur pour la dosimétrie en curiethérapie. *Ann. Phys. Biol. et Méd.* 2 (1967) 139.

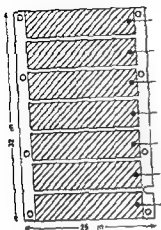


Fig 2 Inner electrode with the seven graphite sections of the transmission chamber

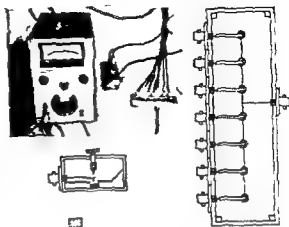


Fig 3 Switch to 7 sectioned transmission chamber. The striped areas indicate the insulator

The oesophagus is surrounded by tissue of variable thickness with an average density of 1 g/cm^3 . Deviations from calculations by the TAR method thus ought to be of somewhat less importance than for a tumour situated in the lung parenchyma. However the investigation has shown that this decrease in the dose due to reduced scattering is still quite observable.

Mathematical calculations for each treated patient would be time consuming and uncertain. Often a relatively long cylinder extending through most of the thorax of the patient and including varying amounts of lung parenchyma is irradiated. The heart and the diaphragm may be included in the radiation beam.

The aim of this investigation has been to calibrate different transmission values by simultaneous measurements in the oesophagus and in the transmitted beam. These calibrations can then be used to calculate the target dose in roentgen rotation treatment of oesophageal tumours and to estimate the variation of the dose in the cranio-caudal direction. In this way the unevenness of the dose can be eliminated by means of compensating filters.

Transmission (T) is here defined as the ratio between the exposure rate of the primary radiation transmitted through a patient measured at some point beyond him and the exposure rate of the primary beam itself at the same point.

The treatment technique includes the following technical data: focus-axis distance 60 cm, focus-fluoroscopic screen distance 120 cm, beam quality 200 kV, external filter 0.2 mm copper, which means a first HVL of 0.7 mm Cu. The patient is treated in a sitting position with arms raised over his head.



Fig 1 Transmission chamber placed on the tube side of the fluoroscopic screen

by GANNING (1951) O'CONNOR (1956) as well as JACOBSSON & KNAUER (1956) have discussed two modifying, mutually counteracting factors: reduced attenuation, which increases the dose to the tumour within a region of lower density and reduced scattering, which decreases the dose to the tumour in such a region. O'CONNOR attempted to estimate the influence of each of these two factors, and he has confirmed his calculations in three patients by measurements with small Sievert chambers, placed directly in the oesophagus. JACOBSSON & KNAUER made measurements in a heterogeneous phantom for some special treatment techniques and obtained correction factors due to reduced scattering as well as reduced absorption. DICKSON & MORGAN (1961) employed NEUMANN & WACHSMANN's method of calculation and correlated their calculations with four measurements in patients. The measured values were not very accurate but they nevertheless indicated some agreement with the calculations. KELLER & ROX (1963) published a collection of tissue factors for different depths in the thorax and abdomen based on measurements of exit exposure. DAHL & VIKTERLOF (1960) measured the cranio-caudal variation in transmission with several small condenser chambers and then constructed compensating filters to make the target dose homogeneous along the oesophagus.

The individual ability of the thorax to absorb and to scatter radiation varies considerably. NATHAN & NAIIDORF indicated that there is a variation of 250% in exit exposure for comparable regions of the same thorax thickness in patients. JACOBSSON & KNAUER indicated that the exit exposure may vary considerably when measured with opposite beam directions. Measurements directly in the tumour region are, of course, the most reliable ones. However, even if the tumour is situated in the oesophagus such measurements are not always possible, in six out of the 50 cases included in the present investigation such measurements could not be made.

Calculation of target dose based on water equivalent thickness determined by means of transmission measurements does not take into account the variation in the dose contribution of scattered radiation at the site of tumour. With the rotation technique one is for practical reasons limited to measuring the transmission

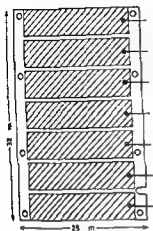


Fig 2 Inner electrode with the seven graph to sections of the transmission chamber

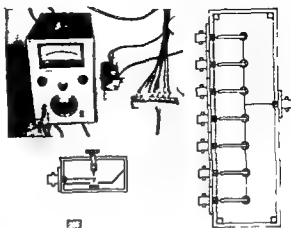


Fig 3 Switch to 7-sectioned transmission chamber
The striped areas indicate the insulator

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The aim of this investigation has been to calibrate different transmission values by simultaneous measurements in the oesophagus and in the transmitted beam. These calibrations can then be used to calculate the target dose in roentgen rotation treatment of oesophageal tumours and to estimate the variation of the dose in the cranio-caudal direction. In this way the unevenness of the dose can be eliminated by means of compensating filters.

Transmission (T) is here defined as the ratio between the exposure rate of the primary radiation transmitted through a patient measured at some point beyond him and the exposure rate of the primary beam itself at the same point.

The treatment technique includes the following technical data: focus-axis distance 60 cm, focus-fluoroscopic screen distance 120 cm, beam quality 200 kV, external filter 0.2 mm copper which means a first HVL of 0.7 mm Cu. The patient is treated in a sitting position with arms raised over his head.

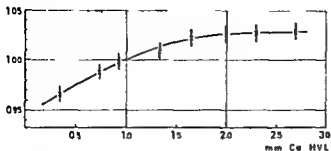


Fig 4 (above) Energy response of the transmission chamber normalized to 1.0 for HVL=10 mm Cu. Vertical lines indicate the spread for different sections of the chamber

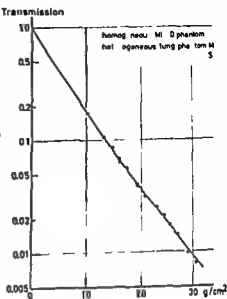


Fig 5 (right) Transmission as a function of phantom thickness in g/cm^2 for a solid mix D phantom and for two heterogeneous lung phantoms HVL=0.65 mm Cu for the primary radiation

Measuring equipment

The ionization chamber which is used to measure the transmission has an area of $25 \text{ cm} \times 32 \text{ cm}$ and is placed in contact with the tube side of the fluoroscopic screen (Fig 1). The construction of this chamber has been previously described (NORDBERG 1962). The walls and the central electrode are made up of 2 mm thick perspex sheets. The inside walls of the chamber are covered with a thin conducting layer of graphite and serve as the other electrode of the chamber. The design of the central electrode is shown in Fig 2. The graphite layer is divided into 7 separate sections, each one having a separate lead through the surrounding metal frame. The chamber has a thickness of about 15 mm and is completely roentgen transparent except for the frame. The outside walls of the chamber are covered with graphite and grounded. The seven leads are joined to a switch situated in the roentgen control room (see Fig 3 for the design of the switch). In the chamber, condensers of 50 000 pF are joined parallel to each section. The total capacity of each section and its corresponding cable is about 200 pF. An electrometer with a low input capacity (5 pF) is used as measuring instrument. A power supply in the control room keeps the inside walls at 300 V and the central electrode is grounded before starting the measurements.

The sections of the central electrode are orientated in a vertical row and each section is 4 cm high and 24 cm wide, thus corresponding to an area of $2 \text{ cm} \times 12 \text{ cm}$ at the place of the rotation axis. The field size at the axis can vary between 4 and 8 cm in width and 10 and 17 cm in height i.e. along the oesophagus.

Table 1

Response per unit field width for different field widths and phantom thicknesses

Field width cm	Equivalent square area cm	A Measurements without grid Phantom thickness, in cm				B Measurements with parallel grid Phantom thickness 10 cm			
		10	15	16	19	10	15	16	19
4	37	1.22	0.76	0.46	0.29	0.87	0.53	0.33	0.21
5	50	1.26	0.76	0.47	0.29	0.88	0.54	0.33	0.21
6	64	1.29	0.77	0.48	0.30	0.89	0.54	0.34	0.24
8	97	1.29	0.79	0.48	0.30	0.89	0.54	0.33	0.21

The irradiated area of each section is directly proportional to the width of the field. When short treatment fields are used the outer sections of the chamber will be hit only by the penumbra of the radiation beam. The charge that each section accumulates during the treatment of a patient is the measure of the exposure caused by the energy fluence from a horizontal cross-section of the patient approximately 2 cm thick during a certain number of full revolutions, a presumption being that scatter contribution from other sections can be neglected.

The quality of the primary radiation corresponds to a first half value layer of about 0.7 mm Cu. The first half value layer of the transmitted radiation measured in broad beam geometry is between 1.5 and 3 mm Cu depending on the thickness of the patient. The response of the chamber (normalized to 1 for the mean value of the response of the sections for a half value layer of 1 mm Cu) is shown in Fig. 4 as a function of the quality of the irradiation. The energy dependence is negligible within the quality range of interest for all practical purposes. The variation in the response between the different sections (indicated by a vertical line in Fig. 4) can also be neglected. The variation in sensitivity from one section to another is probably due to the slightly varying height of the graphite sections.

For the low exposure rate at the place of the chamber less than 2 R/min no loss takes place because of the recombination for a field strength of about 700 V/cm. For accurate measurement of the transmission the chamber must not be hit by scatter radiation from the patient. The ionization chambers usually have a distance of between 40 and 50 cm to the patient. After the beam has passed through 10 cm of water the ratio between the fluence of scattered photons leaving the phantom in directions aiming at a given point in the chamber and the fluence of primary photons towards this same point is about 0.06. The variation of the secondary contribution from the smallest to the largest field used is

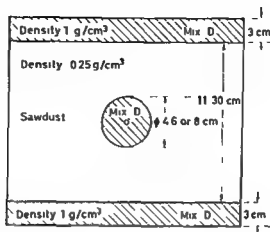


Fig 6 Cross section of the lung phantom used for the calibration

within $\pm 30\%$. After the beam has passed through 15 cm of water, this ratio is twice as much as for 10 cm. The influence of the variation in area is the same (BJARNICARD & HEDTINGER 1961, LECARF 1964).

If the chamber is hit only by primary radiation the response per unit field width should be constant for different field sizes provided the exposure rate is constant all over the cross section of the roentgen beam. This quotient, determined for 4 different field widths and 4 different thicknesses of a homogeneous mix D phantom, is given in Table 1-A. The values for each size of the phantom lie within $\pm 2\%$. This experimental series was repeated with a parallel grid (62 lamellae inch ratio 1:5.5) in front of the transmission chamber (Table 1-B). In this case the spread is within $\pm 1.5\%$. The influence of the grid, measured as the relation between the quotient with grid and the quotient without grid for all field widths and all phantom sizes, lies within 0.69 and 0.72. This reduction corresponds approximately to the grid attenuation of the primary photons. This variation in sensitivity and grid effect for different areas and phantom sizes is so small that the contribution from scattered photons can be considered negligible.

Determination of the transmission through homogeneous mix D blocks and heterogeneous lung phantoms (mix D, sawdust) of different thicknesses with a beam aperture of 5° (Fig 5) gives a first half value layer for the primary radiation of about 3.7 cm mix D corresponding to a monoenergetic radiation of about 80 keV. The first half value layer of copper determined with narrow beam geometry and with an ionisation volume of 1 cm^3 gives a value of about 70 keV. The sixth half value layer is about 5 cm of mix D. The HVI limit of the primary

beam is 5.1 cm of water. Since mix D and water are supposed to have the same linear absorption coefficient, the measurements cited give the actual transmission values. Fig. 5 also shows that the attenuation curve is the same for a homogeneous absorber when the thickness is measured in g/cm.

The transmission chamber is placed directly in contact with the tube side of the fluoroscopic screen which consists of a Pertinex plate (0.4 g/cm) causing backscatter radiation to the chamber. This contribution has been experimentally determined to be about 9% for the transmitted beam which is approximately independent of the various radiation parameters employed. For the primary quality the contribution is 12%. These values agree with calculations made from published data (QUIMBY & LAURENCE 1940; WACHSMAN & DIMOTSIS 1957). Therefore the backscatter contribution merely necessitates a constant correction factor in the determination of the transmission.

The electric charge released during the irradiation is stored in the section itself, the cable and the condenser of the switch. The polarization voltage of the chamber is 300 V and the voltage change of a section will never exceed 30 V. This gives constant sensitivity during the whole irradiation. After irradiation the sections are successively connected with the electrometer by means of the corresponding buttons of the switch. The switch is constructed so as to prevent rubbing of the insulators and as a result it does not contribute to the charge.

Calibration of transmission

Determination of the TAR values corresponding to different transmission values has been made by measurements with heterogeneous lung phantoms of different constructions and by simultaneous measurements in the patients' oesophagi and in the transmitted beam.

1 Calibration by means of phantom measurements. The design of the lung phantom is shown in Fig. 6. It has a central circular mix D cylinder with a measuring channel of about 6 mm diameter. This cylinder is surrounded by saw dust compressed to a volume weight of 0.25 g/cm³ (DAHL & VIKTERLOF 1960) between two parallel mix D blocks each 3 cm thick. The diameter of the mix D cylinder was 4, 6 or 8 cm. For each diameter the total phantom thickness varied from 17 to 36 cm. (The phantoms designated S, M and L have diameters of 4, 6 and 8 cm respectively.) In another series the thickness of the two outer mix D blocks varied from 3 to 11 cm (the phantom being designated by Sa) while the parameters inside the phantom were kept constant. Measurements have been made simultaneously with the transmission chamber and with several condenser chambers in the phantom channel. The phantom was not rotated. The whole series has been repeated for different field widths.

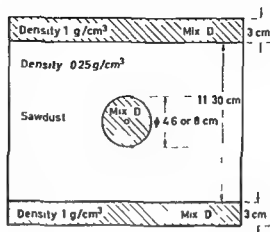


Fig 6 Cross section of the lung phantom used for the calibration

within $\pm 30\%$. After the beam has passed through 15 cm of water, this ratio is twice as much as for 10 cm. The influence of the variation in area is the same (BJARNHARD & HETTINGER 1961, LEGARE 1964).

If the chamber is hit only by primary radiation the response per unit field width should be constant for different field sizes provided the exposure rate is constant all over the cross-section of the roentgen beam. This quotient, determined for 4 different field widths and 4 different thicknesses of a homogeneous mix D phantom, is given in Table 1 A. The values for each size of the phantom lie within $\pm 2\%$. This experimental series was repeated with a parallel grid (62 lamellae/inch, ratio 1.55) in front of the transmission chamber (Table 1 B). In this case the spread is within $\pm 1.5\%$. The influence of the grid measured as the relation between the quotient with grid and the quotient without grid, for all field widths and all phantom sizes, lies within 0.69 and 0.72. This reduction corresponds approximately to the grid attenuation of the primary photons. This variation in sensitivity and grid effect for different areas and phantom sizes is so small that the contribution from scattered photons can be considered negligible.

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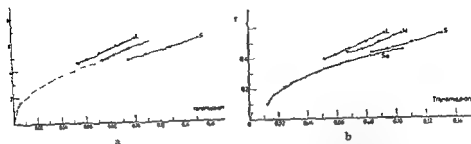


Fig. 8 a) The curves indicated by long and short dashes correspond to those in Fig. 7 calculated for an equivalent square area of 80 cm. The full-drawn curves illustrate phantom measurements for an equivalent square area of 74 cm. L, M and S indicate different phantom constructions. b) The curves indicated by long and short dashes correspond to those in Fig. 7 calculated for an equivalent square area of 40 cm. The full-drawn curves illustrate phantom measurements for an equivalent square area of 42 cm. L, M, S and Sa indicate different phantom constructions.

oesophagus was determined. The condenser chambers are designed for an exposure of about 300 R. Their sensitivity as a function of energy is almost constant ($\pm 1\%$) within the energy interval used. The effective energy of the secondary radiation corresponds to a HVL of about 0.3 mm Cu for the actual irradiation conditions (HETTINGER & LIDEN 1960). The scattered radiation irradiates the chamber almost isotropically. The chamber has a slight radiation direction dependence which causes an increase of the calibration constants of less than 2% (LIDEN 1961).

Results and Discussion

The TAR as a function of the transmission is shown in Fig. 7. The measurement values correspond to the middle part of the treated region of the patients. The values are marked differently for two different intervals of the field size: one interval equivalent to a square area of 40 to 60 cm (\bullet) and the other 60 to 80 cm (\circ) with 19 and 28 points for each interval respectively. One patient had a field size smaller than 40 cm (\circ) and another had a field size larger than 80 cm (\times). The full-drawn line in Fig. 7 is a second degree curve with coefficients calculated from the point lattice by means of the least square method ($T \approx 0.41$ (TAR) ~ 0.014 (TAR)). The two curves indicated by short dashes have been drawn with TAR values calculated from the British Journal of Radiology Suppl. 10 for field sizes of 40 and 80 cm respectively (ref. 5). The relative spread of these two curves for different values of transmission has been transformed to the full-drawn curve and is indicated by long dashes on either

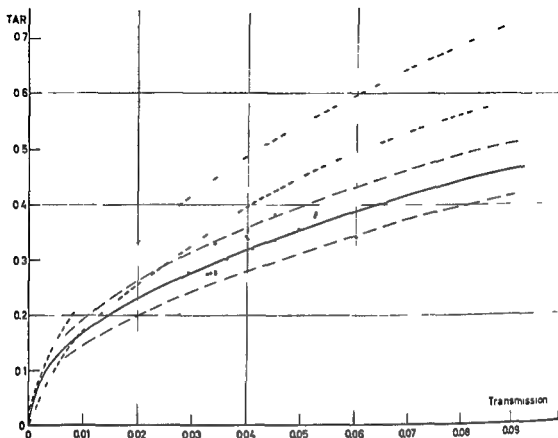


Fig 7 TAR as a function of the transmission indicating patient's measurements field sizes equivalent to square areas of 40 to 60 cm² (●) 60 to 80 cm (○) > 80 cm (×) < 40 cm (○). The full drawn curve $T=0.44(TAR)^2-0.014TAR$ has been calculated to fit the measurements. Curves indicated by short dashes have been calculated for homogeneous material and for equivalent square areas of 10 cm (lowest curve) and 80 cm respectively. The curves indicated by long dashes have been calculated to give the same relative spread for field size variation of experimental full drawn curve.

2 Calibration by means of patient measurements Calibration measurements have been made for all the patients during a continuous period of about 2 years (1960—1962), except in six patients in whom oesophageal measurements could not be made. At least three reliable measurement values are recorded for each patient. The catheter normally contains 2 small condenser chambers and 3 indicators, permitting localization of the measuring catheter on the fluoroscopic screen. Sometimes even a roentgen film has been exposed to check the position of the catheter. Only those measuring values have been used where the oscillation of the catheter was small and the measuring points could be localized within ± 0.5 cm. In this way the dose distribution along the whole treated region of the

sidered valid for 60 cm by correcting for areas different from 60 cm in accordance with already tabulated TAR values. Even without this correction 85 % of the measuring points lie within ± 7 % of the curve of calibration.

The measuring points cover a transmission variation from 0.01 to 0.09 and the weights of patients vary between 35 and 95 kg. Attempts to correlate the individual spread in Fig. 7 to weight, age, sex and localization of the tumour have failed. The material is furthermore not large enough to arrive at a significant correlation.

A comparison of TAR transmission curves calculated from the Table in ref. 5 and from patient measurements for the same size of area clearly shows the loss of dose caused by the reduced contribution of scattered radiation from the thorax compared to the contribution from homogeneous material with a density of 1 g cm^{-3} at the same water equivalent depth.

The phantom measurements have been drawn in Fig. 8a together with both curves for the maximal area in Fig. 7 and in Fig. 8b together with corresponding curves for the minimal area. The field sizes of the phantom investigations were 74 and 42 cm respectively which measurements approximately correspond with 80 and 40 cm respectively. There are three phantom curves in Fig. 8a indicated by L, M and S corresponding to the diameters of 8.6 and 4 cm of the mix D cylinder. These curves were run before and during the same time interval as the calibration with patients was made and therefore the transmission interval later turned out to have been chosen too high. Nevertheless it is easily seen that the M and S curves lie nearest to the patient curve while as would be expected the L curve lies nearest the curve of the homogeneous material. In Fig. 8b another S curve designated Sa is drawn in addition to the L, M and S-curves; this new curve corresponds to a series of investigations with a constant amount of lung tissue but with varying thicknesses of the outer mix D blocks (Fig. 6). The S curve and the Sa-curve should touch each other for a transmission of about 0.09; however in Fig. 8b the curves run at a distance of 4 % of the TAR value. This discrepancy can easily be attributed to experimental errors e.g. re-packing of sawdust between the two series.

The Sa curve was determined when the actual transmission range was better known and is in agreement with the corresponding patient curve for a transmission of more than 2.5 %.

The TAR can be written as follows

$$\text{TAR} = \text{TAR}_0 B_D$$

where a = field size in cm at measuring point P

TAR = TAR of point P with an irradiated area = $a \text{ cm}^2$ at this point

TAR = TAR of point P with an infinitesimal irradiated area

B_D = dose buildup at point P

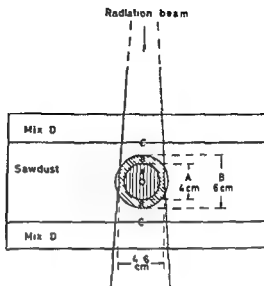


Fig 9 Radiation geometry and different scatter compartments used in the calculation of dose contribution of scattered radiation from different parts around the measuring channel in the phantoms

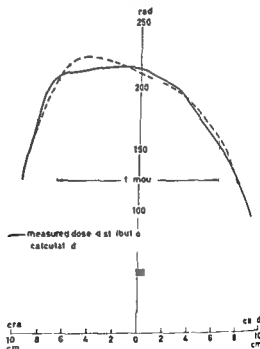


Fig 10 Dose distribution along the oesophagus. The full drawn curve is from measurements directly in the oesophagus and the dashed curve has been determined from transmission measurements

side of the full drawn one. Between these two curves lie 40 points. The total number of points is 47. The two extreme points lie outside this interval. As there is some displacement of the means of the values in the interval 40 to 60 cm and 60 to 80 cm towards smaller and greater IAR, respectively, greater accuracy can probably be achieved if the experimental calibration curve is con-

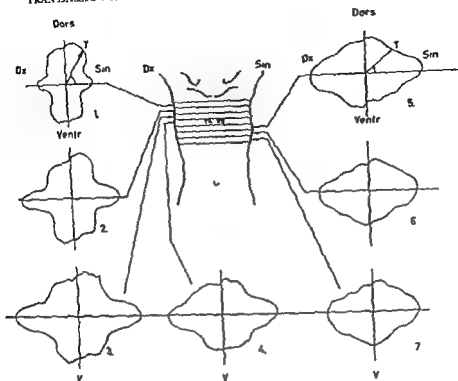


Fig. 11. Transmission variations during a full revolution shown as a polar diagram for each of the seven levels of the thorax indicated in the middle of the figure

centimeter thick around the cylinder in (1) $(B_D-1)_B$ and (3) the remaining irradiated phantom volume $(B_D-1)_C$

If the contribution from a volume is supposed to be proportional to density and if furthermore the change of filtration of the scattered contribution is neglected homogeneous material will get $(B_D-1)_A=0$ for 40 and 80 cm. $(B_D-1)_B$ also remains approximately constant 0.3 while $(B_D-1)_C$ increases from 0.5 to 1.1 in agreement with the corresponding increase of the irradiated volume. This means that the dose contribution of scattered photons from a surrounding cylinder with a radius of 2 cm is between 20 and 25 % of the total dose.

Dose variation along the oesophagus The relation between the transmission and TAR which has been shown in Fig. 7 is only valid in the middle of the irradiated field where B_D is at its maximum. This means that a transmission determined for a point outside the field center would not be directly transferred to

Table 2

TAR variation along a field and corresponding variation in dose contribution from scattered radiation for three different transmissions

Distance from the centre of the field (field length 2r)	TAR TAR _{centre}	$\frac{B_D-1}{(B_D-1)_{\text{centre}}}$		
		Transmission (equiv square area 60 cm ²)		
		0.01	0.04	0.09
1.00 a	0.70	0.6	0.4	0.4
0.75 a	0.91	0.9	0.8	0.8
0.50 a	0.97	1.0	0.9	0.9
0.25 a	0.99	1.0	1.0	1.0
0.00 a	1.00	1.0	1.0	1.0

TAR is calculated from The British Journal of Radiology, Suppl. 10 (ref. 5). In Fig. 5, TAR can be derived from the transmission for half the phantom thickness in g/cm², which gives the actual transmission. This curve, however, is not made with a perfect narrow beam geometry and there are no measuring points in that region of the curve where the interpolation must be done. B_D calculated from the patient curve (equivalent square area 60 cm²), lies between 2 and 3.

TAR₀ is calculated to be 0.234 for transmission of 0.085 (from Fig. 5 about 0.25).

For a field size of 40 cm²

$$\begin{aligned} \text{TAR}_S &= 0.430 \text{ corresponding to } (B_D)_S = 1.84 \\ \text{TAR}_W &= 0.478 \text{ " " } (B_D)_W = 2.04 \\ \text{TAR}_{\text{homogeneous}} &= 0.572 \text{ " " } (B_D)_{\text{max}} = 2.44 \end{aligned}$$

For a field size of 80 cm²

$$\begin{aligned} \text{TAR}_S &= 0.467 \text{ corresponding to } (B_D)_S = 2.00 \\ \text{TAR}_W &= 0.517 \text{ " " } (B_D)_W = 2.21 \\ \text{TAR}_{\text{homogeneous}} &= 0.710 \text{ " " } (B_D)_{\text{max}} = 3.07 \end{aligned}$$

$B_D 1$ can be expressed (Fig. 9) as the sum of the contribution from (1) a cylinder of radius 2 cm around the measuring channel ($B_D 1$), (2) a volume cut out by the geometrical limitation of the radiation beam from a shell one

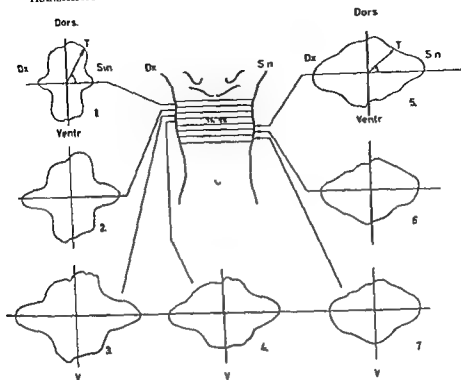


Fig 11 Transmission variations during a full revolution shown as a polar diagram for each of the seven levels of the thorax indicated in the middle of the figure

centimeter thick around the cylinder in (1) $(B_D-1)_B$ and (3) the remaining irradiated phantom volume $(B_D-1)_C$

If the contribution from a volume is supposed to be proportional to density and if furthermore the change of filtration of the scattered contribution is neglected homogeneous material will get $(B_D-1)_A \approx 0.6$ for 40 and 80 cm. $(B_D-1)_B$ also remains approximately constant 0.3 while $(B_D-1)_C$ increases from 0.5 to 1.1 in agreement with the corresponding increase of the irradiated volume. This means that the dose contribution of scattered photons from a surrounding cylinder with a radius of 2 cm is between 20 and 25 % of the total dose.

Dose variation along the oesophagus The relation between the transmission and TAR which has been shown in Fig 7 is only valid in the middle of the irradiated field where B_D is at its maximum. This means that a transmission determined for a point outside the field center would not be directly transferred to

Table 2

TAR variation along a field and corresponding variation in dose contribution from scattered radiation for three different transmissions

Distance from the centre of the field (field length 2a)	$\frac{TAR}{TAR_{centre}}$	$\frac{B_D - 1}{(B_D - 1)_{centre}}$		
		Transmission (equiv square area 60 cm ²)		
		0.01	0.04	0.09
1.00 a	0.70	0.6	0.4	0.4
0.75 a	0.91	0.9	0.8	0.8
0.50 a	0.97	1.0	0.9	0.9
0.25 a	0.99	1.0	1.0	1.0
0.00 a	1.00	1.0	1.0	1.0

TAR is calculated from The British Journal of Radiology, Suppl 10 (ref 5). In Fig 5, TAR can be derived from the transmission for half the phantom thickness in g/cm², which gives the actual transmission. This curve, however, is not made with a perfect narrow beam geometry and there are no measuring points in that region of the curve where the interpolation must be done. B_D calculated from the patient curve (equivalent square area 60 cm²), lies between 2 and 3.

TAR is calculated to be 0.234 for transmission of 0.085 (from Fig 5 about 0.25).

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For a field size of 80 cm²

$$\begin{aligned} TAR_S &= 0.467 \text{ corresponding to } (B_D)_S = 2.00 \\ TAR_M &= 0.517 \text{ « } (B_D)_M = 2.21 \\ TAR_{homogeneous} &= 0.710 \text{ « } (B_D)_{max} = 3.07 \end{aligned}$$

$B_D 1$ can be expressed (Fig 9) as the sum of the contribution from (1) a cylinder of radius 2 cm around the measuring channel ($B_D 1$), (2) a volume cut out by the geometrical limitation of the radiation beam from a shell one

Development of the method The charge of a chamber section accumulated during a treatment gives an integrated average of the patient transmission in all beam directions through the oesophagus during a full revolution Fig 11 shows a considerable variation in the differential transmission for different angles but the polar diagrams also illustrate the symmetry of opposite directions The measurements are carried out with a heterogeneous lung phantom built on a real skeleton corresponding recordings have also been made for patients The calibration of this differential transmission must be made by continuously recording radiation detectors introduced in the oesophagus (BENNER et coll 1959) The average transmission values for different directions through a patient and the transmission of the average thickness of the cross-section in the same directions agree within 7 % for the patients included in the group investigated

The error caused by the integration can therefore be neglected

SUMMARY

A device for simultaneous measurement of the transmission through a patient at different levels is described Correlation between target dose and transmission is obtained by measurements in phantoms as well as in patients The discrepancy in relation to conventional tissue equivalent calculations are discussed

ZUSAMMENFASSUNG

Eine Vorrichtung für gleichzeitige Transmissionsmessungen in verschiedenen Ebenen eines Patienten wird beschrieben Korrelation zwischen der Herddosis und der Transmission wird durch Messungen in den Phantomen sowie in den Patienten erhalten Die Diskrepanz im Verhältnis zu den gewöhnlichen gewebe äquivalenten Bestimmungen wird diskutiert

RÉSUMÉ

L'auteur décrit un dispositif de mesures simultanées à différents niveaux de la transmission du rayonnement à travers le malade au cours de la roentgénéthérapie rotatoire des tumeurs de l'œsophage Il obtient la corrélation entre la dose à la cible et la dose transmise par des mesures sur des fantômes et sur des malades L'auteur examine les discordances avec les calculs faits au moyen des équivalents de tissus habituels

REFERENCES

- 1 BENNER S RAGNHULT I and GERBERT G Miniature ionization chambers for measurements in body cavities *Phys Med Biol* 4 (1959) 26
- 2 BJÄRNGÅRD H and HETTINGER G Spectra of scattered radiation behind slabs of water irradiated by X rays *Arkiv Fysik* 20 (1961) 517

TAR, valid for this point, by using the curves in Fig 7. For a homogeneous phantom the variation of the transit exposure along the field is relatively small and shows only the penumbra of the primary radiation which is independent of field length while the corresponding variation of dose inside the phantom is considerable. The influence of the penumbra is here the same as for the transit exposure and is therefore relatively small, but the variation of the scattered contribution is important. The TAR variation along the field has been determined for different irradiation geometries and has been found to be very much similar if the distance to the central point is expressed in units of field length (Table 2).

The last columns of Table 2 show the variation of scattered contribution along the field for three different transmissions calculated from corresponding variations of TAR. When calculating the dose distribution, the variation of the primary beam intensity must also be considered.

If the target doses, thus determined, are correlated with simultaneously measured doses in the oesophagus of different patients, there is very good agreement. Fig 10 shows a dose distribution with the accustomed agreement between calculation and measurement in the patient.

Target dose. The TAR values valid for a homogeneous water equivalent thorax have been calculated from cross sections drawn at different levels of the patients included in this investigation. This method results in an underestimation of the target dose, averaging 20 % (extreme values 0 and 40 %). Calculation of the target dose in homogeneous material by means of transmission measurements results, however, in an overestimation of the actual dose by between 20 and 40 %.

The measuring and calculation method now described for the determination of the target dose in rotation treatment has been used for about six years.

Daily measurements of the transmission along the treatment field constitute a more exact checking of the reproducibility of the treatment than the mere reading of an output monitor in front of the roentgen tube. The transmission is very sensitive to density changes in the patient. An increase of density corresponding to 1 cm of water gives a decrease in the transmission of between 15 and 18 %. The corresponding decrease in the tumour dose is between 7 and 9 %, as calculated from Fig 7. A change in transmission of 10 % corresponds to a change in the target dose of 4 to 5 %. There is sometimes a continuous transmission change in a patient during a treatment session. This causes a corresponding continuous change of TAR, which change has been verified by direct measurements in the oesophagus of several patients. An investigation of these patients from a medical point of view has been performed in order to find some correlation between transmission changes and irradiation effects of different kinds (NORDBERG et coll 1967).

Development of the method The charge of a chamber section, accumulated during a treatment gives an integrated average of the patient transmission in all beam directions through the oesophagus during a full revolution. Fig. 11 shows a considerable variation in the differential transmission for different angles but the polar diagrams also illustrate the symmetry of opposite directions. The measurements are carried out with a heterogeneous lung phantom built on a real skeleton; corresponding recordings have also been made for patients. The calibration of this differential transmission must be made by continuously recording radiation detectors introduced in the oesophagus (BENNER *et coll.* 1959). The average transmission values for different directions through a patient and the transmission of the average thickness of the cross-section in the same direction agree within 7% for the patients included in the group investigated.

The error caused by the integration can therefore be neglected.

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Eine Vorrichtung für gleichzeitige Transmissionmessungen in verschiedenen Ebenen eines Patienten wird beschrieben. Korrelation zwischen der Herddosis und der Transmission wird durch Messungen in den Phantomen sowie in den Patienten erhalten. Die Diskrepanz im Verhältnis zu den gewöhnlichen gewebäquivalenten Bestimmungen wird diskutiert.

RÉSUMÉ

L'auteur décrit un dispositif de mesures simultanées à différents niveaux de la transmission du rayonnement à travers le malade au cours de la roentgenthérapie rotatoire des tumeurs de l'œsophage. Il obtient la corrélation entre la dose à la cible et la dose transmise par des mesures sur des fantômes et sur des malades. L'auteur examine les discordances avec les calculs faits au moyen des équivalents de tissus habituels.

REFERENCES

1. BENNER S., RAGNULT I. and GERBERT G. Miniature ionization chambers for measurements in body cavities. *Phys. Med. Biol.* 4 (1959) 26.
2. BJARNGÅRD B. and HETTINGER G. Spectra of scattered radiation behind slabs of water irradiated by X-rays. *Arkiv Fysik* 20 (1961) 517.

TAR, valid for this point, by using the curves in Fig. 7. For a homogeneous phantom the variation of the transit exposure along the field is relatively small and shows only the penumbra of the primary radiation which is independent of field length while the corresponding variation of dose inside the phantom is considerable. The influence of the penumbra is here the same as for the transit exposure and is therefore relatively small, but the variation of the scattered contribution is important. The TAR variation along the field has been determined for different irradiation geometries and has been found to be very much similar if the distance to the central point is expressed in units of field length (Table 2).

The last columns of Table 2 show the variation of scattered contribution along the field for three different transmissions calculated from corresponding variations of TAR. When calculating the dose distribution, the variation of the primary beam intensity must also be considered.

If the target doses, thus determined, are correlated with simultaneously measured doses in the oesophagus of different patients, there is very good agreement. Fig. 10 shows a dose distribution with the accustomed agreement between calculation and measurement in the patient.

Target dose. The TAR values valid for a homogeneous water equivalent thorax have been calculated from cross sections drawn at different levels of the patients included in this investigation. This method results in an underestimation of the target dose, averaging 20 % (extreme values 0 and 40 %). Calculation of the target dose in homogeneous material by means of transmission measurements results however in an overestimation of the actual dose by between 20 and 40 %.

The measuring and calculation method now described for the determination of the target dose in rotation treatment has been used for about six years.

Daily measurements of the transmission along the treatment field constitute a more exact checking of the reproducibility of the treatment than the mere reading of an output monitor in front of the roentgen tube. The transmission is very sensitive to density changes in the patient. An increase of density corresponding to 1 cm of water gives a decrease in the transmission of between 15 and 18 %. The corresponding decrease in the tumour dose is between 7 and 9 %, as calculated from Fig. 7. A change in transmission of 10 % corresponds to a change in the target dose of 4 to 5 %. There is sometimes a continuous transmission change in a patient during a treatment session. This causes a corresponding continuous change of TAR which change has been verified by direct measurements in the oesophagus of several patients. An investigation of these patients from a medical point of view has been performed in order to find some correlation between transmission changes and irradiation effects of different kinds (NORDBERG et al. 1967).

GASTRO INTESTINAL FUNCTION AFTER ABDOMINAL COBALT IRRADIATION

by

E. RATZKOWSKI and A. HOCHMAN

The gastro intestinal tract is notorious for its radiosensitivity. Death due to total body irradiation is the consequence of damage to the haemopoietic system and with higher doses the digestive system. The radiation effect on the gastro intestinal lining has been studied in animals by QUASTLER (1956), BOND (1950) CONRAD (1954-1956) and others. Data relating to cell survival and the reparative capacity of the rat and mouse intestinal mucosa after continuous and single radiation exposure have been reported by QUASTLER et coll (1959) BLOOM (1950) WILSON (1964), and WIERNICK et coll (1966). Clinical observations in human gastro intestinal reactions following irradiation with injury and complications have been reported by ASHBAUGH et coll (1963), BROWN (1962) WOOD et coll (1963) ROSEN et coll (1964) GRAHAM et coll (1963) HALLS (1955) and others.

During the last ten years isotope labelled substances such as ^{131}I labelled trolein and oleic acid and ^{131}I labelled polyvinylpyrrolidone have become available for the investigation of the absorptive capacity and permeability of the gastro intestinal mucosa following irradiation. Few reports on the func

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- 3 DAHL O and VIETERLOF K J Den fungerande manniskolungans roentgenabsorption en undersokning med sikte på djupdosberäkningar och fantomkonstruktioner (In Swedish) Nord Med 54 (1955), 1576
- 4 — — Attainment and value of precision in deep radiotherapy Acta radiol (1960) Suppl No 189
- 5 DEPTH DOSE TABLES FOR USE IN RADIOTHERAPY Brit J Radiol Suppl No 10 (1961)
- 6 DICKSSON R J and MORGAN R H 250 kV rotation therapy for carcinoma of the oesophagus using the Johns Hopkins screen intensifier Amer J Roentgenol 85 (1961) 78
- 7 FAILLA G The absorption of radium radiation Amer J Roentgenol 8 (1921) 215
- 8 GYNNING J Roentgen rotation therapy in cancer of the esophagus Dosage problems Preliminary results Acta radiol 35 (1951) 428
- 9 HETTINCER G and LIDÉN K Scattered radiation in a water phantom irradiated by roentgen photons between 50 and 250 keV Acta radiol 53 (1960) 73
- 10 JACOBSSON L E and KNAUER J S Correction factors for tumour dose in the chest cavity due to diminished absorption and scatter in lung tissue Radiology 67 (1956) 863
- 11 KELLER H L und ROK JR S Faktoren zur Berücksichtigung nicht wasseraquivalenter Gewebe bei Strahlungen zwischen 200 kV und 17 MeV Strahlentherapie 122 (1963) 531
- 12 LÉGARÉ J M Exit surface dose Correction factors Radiology 82 (1964) 272
- 13 LIDÉN K Depth dose measurement in esophagus in roentgen rotation therapy Acta radiol 30 (1948) 61
- 14 — Errors introduced by finite size of ion chambers in depth dose measurements Selected topics in radiation dosimetry IAEA Wien 1961
- 15 MORGAN R H Handbook of Radiology Year Book Publishers Chicago 1955
- 16 NATHON J R and NAIDOFF C P Comparative study of X ray transmission in thorax and abdomen in living subjects Radiology 58 (1952) 241
- 17 NEUMANN W und WACHSMANN F Ermittlung der Herddosis bei Rotationsbestrahlung unter Berücksichtigung der Absorptionsunterschiede in Gewebe Strahlentherapie 74 (1942) 438
- 18 NORDBERG U B An ionization chamber with several sections for transmission dose measurements Swedish Cancer Society Yearbook 3 p 337 Almqvist & Wiksell Stockholm 1962
- 19 — HENRIKSSON H LANDBERG T et coll Continuous recording of transmission during roentgen irradiation of oesophagus cancer Acta radiol Ther Phys Biol 6 (1967) 432
- 20 O CONNOR J E A transit dose technique for the determination of doses in inhomogeneous bodies Brit J Radiol 29 (1956) 663
- 21 QUIMBY E H COPELAND M M and WOODS R C The distribution of roentgen rays within the human body Amer J Roentgenol 32 (1934) 534
- 22 — and LAURENCE G C The Radiological Society of North America Standardization Committee Techn Bull No 1 Radiology 35 (1940) 138
- 23 ROBBINS R and MESZAROS J The calculation of rotation therapy tumour doses at 250 kV by means of the transmitted dose rate Radiology 63 (1954) 381
- 24 WACHSMANN F und DIMOTIS A Kurven und Tabellen für die Strahlentherapie II 114 S Hirzel Verlag Stuttgart 1957
- 25 WEATHERWAX J L and ROBB C Determination of radiation values in lung tissue with variable qualities of radiation Radiology 14 (1930) 401

ment schedules with field size 20 cm \times 20 cm, or 20 cm \times 16 cm, and 2 000 to 4 000 rad tissue dose, were as follows

	Number of patients
Whole abdomen	34
Lower abdomen (4 fields)	14
Lower abdomen (2 fields)	9
Upper abdomen (4 fields)	10
Upper abdomen (2 fields)	3
No irradiation	5

Method of investigation The following tests were carried out for an evaluation of the functional performance of the gastro intestinal tract

1 Absorption of vitamin B12 labelled by ^{57}Co (SHILLING 1963 test) Urinary excretion of more than 6 % of the orally administered dose was considered normal

2 Fat absorption studied by ^{131}I labelled triolein (SANDERS et coll 1956 REEVES et coll 1959 REITH et coll 1961) Fecal radioactivity expressed as percentage of the dose administered was determined and up to 3 % were considered as normal Blood radioactivity was defined as percentage of test dose per liter of whole blood

3 Determination of macromolecule passage through the intestinal wall protein loss by ^{131}I labelled polyvinylpyrrolidone (GORDON's 1959 PVP test) Up to 1.5 % of the administered dose found in the feces was considered normal

4 Gastric acid secretion After stimulation by the subcutaneous injection of 0.25 mg histamine the total acidity (normal 50 to 100 degrees) and free hydrochloric acid (normal 25 to 50 degrees) were determined

The patients were kept under close clinical observation during the investigation and controlled with blood counts biochemical examinations and the necessary roentgendagnostic procedures

Clinical observations The patients in this series were seriously ill. Large abdominal masses occasionally gave rise to partial obstruction or complete ileus. Diarrhoea during or after treatment in ten patients was probably due to the irradiation. Proctitis was recorded in two patients and in one patient cystitis. In four patients cellulitis of the abdominal wall appeared some time after irradiation. Two patients developed terminal signs of renal damage, possibly irradiation induced. These clinical disturbances corresponded rarely with functional impairment as indicated by the tests. Nearly all patients receiving

tional reaction of the gastro intestinal mucosa to therapeutic irradiation with telecobalt have been published, however (REEVES et coll 1963, 1965, GOODRICH et coll 1962)

The aim of the present investigation was to ascertain functional changes of the gastro intestinal tract in patients suffering from abdominal carcinomatosis who received telecobalt therapy, each received 2 000 to 4 000 rad homogenous irradiation to a large part of or to the whole abdomen

Material and Treatment Seventy five patients (67 females and 8 males) suffering from widespread malignancy of the abdomen were investigated. The mean age was 50.1 (range 12—78). The diagnoses in the 75 patients were as follows

	Number of patients
Carcinoma of ovary	37
Carcinoma of uterus	5
Carcinoma of cervix	3
Generalized abdominal spread of unknown origin	1
Carcinoma of breast with general abdominal spread	4
Carcinoma of colon	3
Carcinoma of stomach	3
Carcinoma of rectosigmoid junction	2
Mesothelioma peritonei	1
Abdominal lymphoma	2
Splenic lymphoma	1
Reticulum cell sarcoma of stomach	1
Hodgkin's disease	4
Leiomyosarcoma	2
Neuroblastoma	1
Carcinoma of pancreas	2

In fifty five patients the diagnosis was established by laparotomy, in seven patients cytologically from aspirated abdominal fluid, in eleven patients by biopsy and in two on the clinical evidence. The mean survival of fifty four patients was 23 months (median survival 13 months, range 2—228 months). Eighteen patients were alive 3 months to 13 years after the diagnosis was established, for three patients the survival time was unknown.

The patients received cobalt 60 teletherapy in accordance with the clinical findings either to the lower or upper, or to the whole abdomen. The treat-

ment schedules, with field size 20 cm \times 20 cm, or 20 cm \times 16 cm and 2 000 to 4 000 rad tissue dose were as follows

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Table 3

Results of Schilling test in relation to irradiated area and irradiation doses

Irradiation area	Irradiation dose 800—2 000 rad				Irradiation dose over 2 000 rad			
	Total number of tests	Number and abnormal tests	Mean excretion %, of		Total number of tests	Number and abnormal tests	Mean excretion of	
			Ab	All normal tests			Ab-normal tests	All tests
Lower abdomen	11	3 (36.5)	4.5	10.6	26	8 (30.8)	2.7	11.2
Upper abdomen	4	1 (25)	4.1	15.2	8	3 (37.5)	3.9	8.5
Whole abdomen					16	5 (31.3)	3.2	9.92

Table 4

Schilling tests repeated in the same patient

Results of repeated tests	Dose of radiation in rad			Time difference of 18 months between tests
	800—2 000	2 000—3 000	< 3 000	
	Difference between test and test	Dose difference	Dose difference	
No change	3	1	1	
From normal to abnormal	3	1		1
From higher to lower excretion	2	1		
From lower to higher excretion	2	1		

ed and often only one of the gastro intestinal functions could be investigated. This made it difficult to arrive at an accurate evaluation of the results.

Schilling test Seventy-two tests were performed in 40 patients and twenty of these were abnormal (27.7%). The results of the Schilling test at different radiation levels are given in Table 1, and the influence of the time interval after irradiation on B12 absorption is recorded in Table 2. The results of the Schilling test in relation to the irradiated area and the irradiation dose are given in Table 3.

Of the nine Schilling tests performed before irradiation only four were repeated in the same patient during treatment: two gave no change after

Table 1

Results of the Schilling test at different dose levels

Radiation rad	Total tests	Abnormal tests		Mean excretion in per cent	
		Number	Percentage	Abnormal tests	All tests
None	9	—	—	—	17.45 (range 7.4—35.6)
800—2 000	12	4	33.3	5.02	11.9 (range 4.1—35.5)
2 000—3 000	28	9	32.1	3.0	10.5 (range 0.5—23.7)
< 3 000	23	7	30.4	3.21	10.75 (range 1.5—25)

Table 2

Irradiation of abdominal cavity with 2 000 rad and more — Schilling test performed at different time intervals

Time after irradiation	Number of tests	Number abnormal	Percentage abnormal	Percentage mean excretion	
				Abnormal tests	All tests
Within 1 week	30	11	36.6	3.18	10.07 (range 0.5—25.0)
1 to 12 months after treatment	10	2	20	3.3	12.66 (range 2.4—23.7)
1 to 10 years after treatment	11	3	27.3	2.6	8.9 (range 1.5—15)

irradiation to the upper abdomen complained of anorexia or nausea, no marked clinical changes were recorded.

Leucopenia was the main radiation induced complication, leading to protraction or interruption of the treatment. This was particularly prominent in the irradiation of the lower abdomen. Thirty patients receiving 3 000 rad to the lower abdomen had a mean leucocyte count at the beginning of the treatment of $6\,744/\text{mm}^3$ but at the end of the treatment there was a mean drop of 42.5 %.

The aim was to follow the patients during and after treatment and to establish the functional ability of the gastro intestinal tract before the commencement of therapy and following various doses of radiation. The study was however carried out on very ill patients and treatment had often therefore to be started before any tests were possible. Tests could sometimes not be repeat

Table 3

Results of Schilling test in relation to irradiated area and irradiation doses

Irradiation area	Irradiation dose 800—2 000 rad				Irradiation dose over 2 000 rad			
	Total number of tests	Number and abnormal tests	Mean excretion of		Total number of tests	Number and abnormal tests	Mean excretion of	
			Abnormal tests	All normal tests			Abnormal tests	All normal tests
Lower abdomen	8	3 (36.5)	4.5	10.6	26	8 (30.8)	2.7	11.2
Upper abdomen	4	1 (25)	4.1	15.2	8	3 (37.5)	3.9	8.5
Whole abdomen					16	5 (31.3)	3.2	9.92

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Schilling tests repeated in the same patient

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	800—2 000 Difference between test and test	2 000—3 000 Dose difference	< 3 000 Dose difference	
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Of the nine Schilling tests performed before irradiation only four were repeated in the same patient during treatment: two gave no change after

Table 5

Fecal excretion of ^{125}I labelled triolein before irradiation and at different radiation levels

Irradiation rad	Mean fecal excretion %	Range %	Number of examinations	Number and % of abnormal tests	Mean fecal excretion in % of	
					Abnormal tests	Normal tests
All examinations	1.96	0.07—26.2	76	32 (42.1)	10.14	1.18
Before irradiation	4.28	0.2—12.2	11	4 (36.3)	9.27	1.46
After 800 and over	5.08	0.07—15.6	65	28 (43)	10.2	1.14
600—1 000	6.57	0.1—18.1	7	1 (57.1)	10.2	1.7
After 2 000	5.22	0.07—26.2	52	22 (42.3)	10.4	1.18
After 3 000 and over at least 3 months previously	3.88	0.07—10.8	15	7 (46.6)	6.9	1.23

Table 6

Results of ^{125}I labelled triolein excretion test in relation to the irradiated area — Irradiation dose 2 000 rad and over

Irradiated area	Number of tests	Number of abnormal tests	Per cent of abnormal tests	Mean excretion in per cent of		
				All tests	Abnormal tests	Normal tests
Lower abdomen	29	9	31	4.01	10.2	1.21
Upper abdomen	6	2	33.3	2.91	6.6	1.0
Whole abdomen	20	12	60	7.06	11.22	0.84

3 000 rad to the lower and 3 000 rad to the whole abdomen, in one test excretion of the isotope became abnormal after 3 500 rad to the upper abdomen, and in one it changed from 35.6 % to 13.6 % after 3 000 rad to the whole abdomen.

Sixteen patients underwent B12 absorption examinations during treatment, the results of these are presented in Table 4.

Six patients with abnormally low urinary excretion of the isotope were re-examined with due regard to the intrinsic factor. Three of these then had normal excretion, i.e. only three of the six patients suffered from malabsorption but the three others had enzyme deficiency.

Table 7

Comparison of fat absorption responses at different radiation levels (changes in fecal excretion) in sixteen patients who underwent repeat examinations

	After dose differences of		Upper abdominal added to lower abdominal irradiation	After time interval of 2 to 6 months
	2 000—3 000 rad	Over 3 000 rad		
Normal and no change	4		1	1
From normal to abnormal	1		4	1
From abnormal to normal		1		2
Abnormal no change		1		

Table 8

Mean blood radioactivity in 64 patients after trolein test dose

Kind of patients examined	Number of examinations	Mean radioactivity μ l			Range per cent
		Mean after 4 hrs	Mean after 5 hrs	Mean peak within first 6 hrs	
All	64	2.43	2.68	2.80	0.7—5.8
Patient with normal fecal excretion	36	2.52	2.61	2.88	0.9—5.8
Patients with abnormal fecal excretion	27	2.26	2.52	2.66	0.7—5.61
Before irradiation	8	2.31	2.8	2.8	0.98—4.6
Irradiation 800 rad and over	57	2.07	2.62	2.77	0.7—5.8
Irradiation 2 000 rad and over	45	2.32	2.51	2.74	0.8—5.5
3 000 rad and over at least 3 months previously	13	2.69	2.77	2.98	1.1—5.61

⁵¹I labelled trolein fat absorption studies Examinations were carried out in 52 patients thirty seven of which (45.1%) had an abnormally high fecal excretion. Twenty eight out of the fifty two patients (53.8%) had fat malabsorption at some time during the investigation. The mean fecal excretion in all the tests performed was 6.7% with a range of 0.07%—82%.

Among the 52 patients examined for fat absorption two were suffering from generalized abdominal lymphoma, two from abdominal Hodgkin's disease and one patient from pancreatic carcinoma with spread into the gastric

Table 5

Fecal excretion of ^{125}I labelled trolein before irradiation and at different radiation levels

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					Abnormal tests	Normal tests
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Irradiated area	Number of tests	Number of abnormal tests	Per cent of abnormal tests	Mean excretion in per cent of		
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Table 10

Gastric acid secretion at various radiation levels

Irradiation rad	Total acidity				Free acidity				Ab- normal
	Normal	Hyper	Hypo	An acid	Normal	Hyper	Hypo	An acid	
None	4	2	1		4	2	1		3/7
800-2 000	1		7		1		5	2	42 8 7/8
2 000-3 000	5		6		5		2	4	87 5 6/11
Over 3 000	1		4	1	1		1	4	54 5 5/6
Total	11	2	18	1	11	2	9	10	83 3 21/32 63 6

32 abnormals 10.14 % (range 3.3 %—26.2 %). The fecal excretion of triolein at different radiation levels is recorded in Table 5.

The fat absorption results in relation to the irradiated area are presented in Table 6.

Four of the triolein examinations performed before irradiation, were repeated in the same patients after irradiation with 3 000 rad. The fecal excretion in these four patients were before irradiation 2.5 %, 0.7 %, 5.7 % and 0.4 % respectively. The repeat triolein tests gave the following values 14.1 %, 1.8 %, 26.2 % and 0.2 % respectively.

Sixteen patients were re-examined during and after irradiation the doses employed ranging from 1 000 to 4 000 rad. The fat absorption responses according to the triolein test are given in Table 7. Nine patients suffered from diarrhoea and one from proctitis during or after treatment. Six of these had at some time abnormal fecal triolein excretion while in four patients the test was within normal limits.

The blood radioactivity was determined in 64 patients the mean peak value during the first 6 hours after the test meal for all patients being 2.08 %/l. Nineteen patients reached the maximum level within 4 hours, thirty three within 5 hours and twelve patients within 6 hours. The blood radioactivity in patients with normal and abnormal fecal excretion at different doses is summarized in Table 8.

Six examinations were carried out in the five patients excluded (four patients with abdominal lymphatic disease and one with carcinoma of the

Table 9

Faecal PIP excretion, radiation dose and clinical data in five patients with protein loss

Case	Excretion %	Irradiation dose rad	Clinical data
1	1.6	2 000 to lower abdomen	Generalized abdominal malignancy of ovarian origin some diarrhoea during treatment proteins normal
	0.9	3 000 to lower 1 800 to upper abdomen	
28	6	2 100 to lower abdomen	Generalized abdominal malignancy of ovarian origin poor general condition during treatment septic temperature
38	0.5	1 400 to lower abdomen	Abdominal malignancy due to ovarian carcinoma good general condition at beginning of treatment albumin/globulin ratio 3.8/2.8
	4.5	3 000 to lower 2 000 to upper abdomen	Two weeks after treatment severe diarrhoea death at 6 months after treatment from uremia probable renal damage albumin/globulin ratio 3.8/2.6
40	1.9	Before irradiation	Generalized abdominal lymphoma cachexia diarrhoea albumin/globulin ratio 2.9/2.8
	0.25	2 000 to lower abdomen	No improvement
45	0.6	3 000 to lower abdomen	Carcinoma of rectosigmoid junction 50 cm of large bowel resected
	0.03	3 000 in lower 2 000 to upper abdomen	
	4.9	5 500 to lower 2 400 to upper abdomen	Diarrhoea during treatment

lumen and bowel The prominent symptom of three of these patients was persistent diarrhoea.

Intestinal lymphoma is frequently associated with fat malabsorption, as has been described in a number of reports (Gough et coll. 1962, Spracklen 1963, Ramot et coll. 1965). Five patients were therefore excluded from the study since they were considered unsuitable for assessing radiation induced functional changes. The results of the examinations of these five patients will however be given separately below.

Seventy-six triolein examinations were carried out in the remaining 17 patients, and thirty-two of these (42.1%) were abnormal. The mean faecal excretion of all the 76 tests was 4.96% (range 0.07%–26.2%). The mean faecal excretion in 44 normal tests was 1.18% (range 0.07%–3%), and in the

for the intestinal mucosa. Animal experiments are made with continuous exposure or with large single exposures at different dose levels and cannot be compared with fractionated and protracted therapy in human subjects.

In evaluating the present study we met with another difficulty. Only a limited number of baseline data (pre-treatment levels) for our own patients could be obtained, the reasons being given above. Moreover, progress of the disease or its improvement following treatment are factors likely to influence the performance of the gastro-intestinal tract and have to be taken into consideration. The data obtained in this study seem however to permit reliable conclusions as to whether therapeutic cobalt irradiation causes severe impairment of the gastro-intestinal function or not. No severe clinical side effects were observed apart from leukopenia which produced no serious haematologic complications.

B₁₂ absorption. Irradiation caused impairment of the B₁₂ absorption (Table 1) in about a third of the patients. With rising dose levels impairment in these susceptible patients increased as shown by the mean abnormal urinary excretion which fell from 5.02 % to 3 %.

The time factor (Table 2) appears to have some influence as the percentage of patients affected by B₁₂ absorption disturbance fell to less than 20 % 11 months after cessation of therapy. The severity of impairment did not alter.

What part of the abdomen was irradiated had no influence on the B₁₂ absorption (Table 3) but again higher dose levels caused more severe disturbances. Furthermore repeated Schilling tests indicated that added radiation doses affected the B₁₂ absorption in more than 30 % of the patients (Table 4). Because of the small number of tests modified by the intrinsic factor no conclusion can be drawn as to whether enzyme deficiency can be caused by irradiation.

Fat absorption. It is more difficult to judge the results of the fat absorption examinations since four (36.3 %) of the eleven tests performed before treatment was started were abnormal. Tables 5, 6 and 7 suggest however that fat absorption impairment be caused by irradiation within the therapeutic dose range in about 25 % of the patients.

The tabulated data further indicate (1) that the mean fecal excretion of the isotope is considerably higher after than before irradiation, (2) the mean fecal excretion of patients with fat malabsorption is higher after irradiation than before, (3) the percentage of abnormal tests is higher after irradiation than before, the peak being in the dose range 600 to 1 000 rad, (4) three months after irradiation the percentage of abnormal tests does not change much but

pancreas), the mean fecal excretion was 28.7 %. Four of the tests were performed before irradiation, one after 2 000 rad (9.3 %) and one after 3 500 rad (1.9 %). The blood radioactivity was determined in four of the patients. The one patient, with normal fecal excretion, had the same blood radioactivity (2.5 %/l and 2.8 %/l) as was noted earlier in the other patients (see p. 423). The three patients with severe fat malabsorption had a much lower blood radioactivity, the mean peak being at 4 hours 0.85 %/l, at 5 hours 1.41 %/l, and at 6 hours 1.54 %/l.

PVP test as an indicator of protein loss from the digestive tract. Fifty-one PVP examinations were carried out in 39 patients, five tests (9.1 %) indicated abnormally high fecal excretion of isotope. The mean fecal excretion in all the 51 examinations was 0.84 % (range 0.03 %—6 %). In the 46 normal tests, the mean fecal excretion was 0.52 % (range 0.03 %—1.5 %), in the five abnormal tests 3.7 % (range 1.6 %—6 %).

Repeat PVP tests were performed in 10 patients including four patients who at some time of the investigation had abnormal permeability of the gastrointestinal mucosa for macromolecules. The results of the various tests in patients, representing protein loss, radiation doses and clinical details, are summed up in Table 9.

Gastric acid secretion. Thirty-two gastric acid examinations were carried out in 24 patients, twenty-one of the examinations (65.6 %) revealing abnormal values. The total acidity tests in these patients revealed hyperacidity in 2, hypoacidity in 18, and anacidity in one patient, while the free acidity tests disclosed hyperacidity in 2, hypoacidity in 9, and anacidity in 10 patients.

Correlation of the various irradiation doses to gastric acid secretion rendered the results reported in Table 10. The gastric acid examinations were repeated in six patients. Further irradiation diminished the gastric acid secretion. The gastric acidity returned to normal 6 months after irradiation in one patient.

The four tests (Schilling, triolein, PVP gastric acid secretion) were, as previously mentioned, carried out in 75 patients. In 4 patients, all four of the tests, in 26 three, and in 14 patients two of the tests were applied, and sixteen out of 47 patients (34 %) had gastrointestinal dysfunction proven by different parameters.

Discussion

No series of normal healthy people can receive high doses of abdominal irradiation for comparison, and investigations in irradiated healthy animals can be correlated only in so far as they demonstrate a good recovery potential.

for the intestinal mucosa. Animal experiments are made with continuous exposure or with large single exposures at different dose levels, and cannot be compared with fractionated and protracted therapy in human subjects.

In evaluating the present study we met with another difficulty. Only a limited number of baseline data (pre treatment levels) for our own patients could be obtained, the reasons being given above. Moreover, progress of the disease or its improvement following treatment are factors likely to influence the performance of the gastro intestinal tract and have to be taken into consideration. The data obtained in this study seem however to permit reliable conclusions as to whether therapeutic cobalt irradiation causes severe impairment of the gastro intestinal function or not. No severe clinical side effects were observed apart from leukopenia which produced no serious haematologic complications.

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the mean fecal excretion in the abnormal tests is much lower, perhaps indicating recovery. The follow-up examinations were however insufficient in number to determine recovery or delayed effects of irradiation on fat absorption.

The highest percentage of abnormal examinations and the highest mean abnormal excretion occurred after irradiation of the whole abdomen.

Some comparable data appear in the literature. SANDERS *et coll.* (1956) found transient malabsorption in 13 out of 29 patients after 200 kV roentgen irradiation within a dose range of 945 to 3 100 R, the highest incidence occurring during the third week after 2 000 R. REEVES *et coll.* (1959, 1963) confirmed the incidence of fat malabsorption after irradiation, with a greater percentage of abnormal tests after telecobalt than after conventional therapy; the authors reported the majority of abnormal triolein absorption tests after 2 000 rad and during the third week of therapy. The investigations of GOODRICH *et coll.* (1962) indicated a very low incidence of fat malabsorption as determined by the oleic ¹⁸¹I absorption tests; only the lower abdomen was irradiated in these studies.

The mean blood radioactivity as well as the mean peak blood values (according to Table 8) were within the normal range even in patients with abnormal fecal triolein excretion. It has been pointed out by many authors (CORREIA *et coll.* 1963, ISLIV *et coll.* 1963, REEVES *et coll.* 1963) that fecal triolein excretion is a more reliable indicator of fat absorption disturbance than blood radioactivity.

Very low blood levels have been described as significant of triolein malabsorption (CORREIA *et coll.*), an observation confirmed in the patients of the present series with abdominal lymphoma and pancreas carcinoma. Not only did these patients have a much higher fecal triolein excretion than all the other patients, but their blood radioactivity was significantly lower, 0.85 %/l as against 2.85 %/l.

Protein absorption. Only 9.8 % of the PVP examinations gave abnormal results, suggesting that the macromolecule passage through the mucosal barrier is only rarely affected by irradiation. The analysis of the abnormal results (Table 9) indicates that Case 1 improved with additional irradiation. Case 38, a patient who died from uremia following irradiation, might have had a particular hypersensitivity affecting not only the gastro-intestinal tract. Case 40 was one of the lymphoma patients excluded from the evaluation of fat absorption; he failed to improve clinically after irradiation but according to the PVP test no longer suffered from macromolecule loss. Case 45 developed abnormal fecal excretion only after a high irradiation dose; resection of a large

part of the bowel must however be considered as a contributory cause of malabsorption in this instance

We have found no comparable investigations in human subjects in the literature in animal experiments radiation caused protein loss through the gastro intestinal wall in the dose range 250 to 1 000 rad (SULLIVAN 1960)

Gastric acid secretion The influence of irradiation on the gastric acid secretion has been recognized for many decades (CASE et coll 1928 PALMER et coll 1939) and as doses of 1 000 to 2 500 R have produced transient anacidity in two thirds of patients this radiation effect has been used as treatment in peptic ulceration (RICKETS et coll 1948) About two-thirds of the present examinations had abnormal values (Table 10) but as differences at various radiation levels were insignificant no dose relationship could be established as little as 800 rad however induced hypoacidity Gastric acidity returned to normal in one patient 6 months after 3 000 rad The point of recovery has not been especially investigated in this study as it has been established previously

When evaluating the results of the four different tests, a differential radiosensitivity of the gastro intestinal tract in its absorptive capacity for various substances appears to exist B12 and fat absorption are more often impaired than protein absorption These conclusions are supported by the multiple investigations carried out in the same patients Gastric acid secretion is easily influenced by irradiation, but the relation to the other tests could not be established directly in the study as gastric secretion was often the sole test carried out in a given patient

The relatively minor functional impairment of the gastro-intestinal tract in the human material corresponds well with observations in animal experiments on intestinal cell survival and irradiation response QUASTLER et coll (1959) demonstrated experimentally that the intestinal mucosa of the rat at dose rates up to 415 rad per day maintained normal crypt size generation time and mature cell life span, at 415 rad per day however, the percentage of proliferating cells diminished This steady state failed to change with a continuation of the irradiation and it is quite possible that no functional disturbance ensued WILSON (1964) interpreted the experimental results of QUASTLER on the basis of cell survival data and reached the same results as the latter by calculation WIERNICK (1966) studied the effect of various fractionated irradiation regimes in human subjects by jejunal biopsies after a single dose of 1 000 rad the intestinal mucosa was damaged beyond repair This corresponds with the threshold dose reported by QUASTLER (1956) and QUASTLER & ZICKER (1959) causing the intestinal syndrome I and intestinal syndrome II and the death of the animal With two weekly doses of 500 R

and six treatments spread over 18 or 19 days, WIERNICK *et coll* (1966) obtained progressive recovery of the jejunal mucosa in human subjects. He proposed a fractionation method consisting of large doses spread in such a way as to enable sufficient recovery of the intestinal lining and controlled by repeated biopsies. He hoped thereby to produce greater tumour destruction.

All these investigations did not deal with the functional state of the gastro intestinal tract but they explain why therapeutic telecobalt irradiation according to our results gave rise to an impairment of the gastro intestinal functional capacity, which generally resulted in only mild disturbances in a limited number of patients. This negative finding is of practical importance as it enables the continuation of an effective palliative treatment measure. The results may perhaps be further improved by larger fractionations controlled by repeated biopsies and functional studies.

Conclusions

Seventy five patients with generalized abdominal malignancy were given therapeutic telecobalt irradiation to a part or the whole of the abdomen with 2 000 to 4 000 rad. The functioning condition of the gastro intestinal mucosa was studied by B₁₂ absorption, triolein absorption, PVP and gastric acid secretion tests.

The B₁₂ absorption was impaired in about one third of the patients to a degree directly related to the dose. The number of patients affected began to diminish one month after the cessation of treatment. The fecal triolein excretion was high in about 25 per cent of the patients, the peak excretion being in the dose range 600 to 1 000 rad. The greatest percentage of abnormal tests and highest mean abnormal fecal excretion were noted after the irradiation of the whole abdominal cavity. The blood radioactivity was not a sensitive indicator of fat malabsorption. The PVP test revealed almost no macromolecule loss through the gastro intestinal mucosa in the therapeutic dose ranges. The gastric acid secretion was diminished in about two thirds of the patients after more than 800 rad but the restoration to normal acid levels occurred in most of them.

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SUMMARY

Therapeutic telecobalt irradiation with 2 000 to 4 000 rad was administered in 75 patients with generalized abdominal malignancy. The effect upon the intestinal mucosa as indicated by the B₁₂ absorption, triolein absorption, PVP and gastric acid secretion tests is discussed.

ZUSAMMENFASSUNG

Tellocobaltbestrahlung von 75 Patienten mit generalisierter abdomineller Malignität wurde mit Dosen von 2 000 bis 4 000 rad vorgenommen. Der Einfluss der Bestrahlung auf die Darmschleimhaut mit Bezug auf die Vitamin B₁₂ Absorption, Trioleinabsorption, PVP und die Sekretion der Magensaure wird diskutiert.

RÉSUMÉ

Une série de 75 malades atteints d'affection maligne généralisée de l'abdomen ont été traités par télécobalt, thérapie par des doses de 2 000 à 4 000 rad. Les auteurs en ont étudié l'effet sur la muqueuse intestinale au moyen de l'absorption de la vitamine B₁₂, l'absorption de la trioléine, de PVP et par des épreuves de la sécrétion acide gastrique.

REFERENCES

- ASHBALGH D. G. and OWENS J. L. Intestinal complications following irradiation for gynecological causes. *Arch Surg* 87 (1963) 100.
- BLOOM M. A. Acquired radioresistance of the crypt epithelium of the duodenum. *Radiology* 55 (1950) 104.
- BOND V. P., SWIFT M. N., ALLEN A. C. and FISHLER M. C. Sensitivity of the abdomen of rat to X irradiation. *Amer J Physiol* 16 (1950) 323.
- BROWN F. A. Gastro-intestinal complications associated with radiation therapy. *Amer J dig Dis* 7 (1962) 1006.
- CASE J. T. and BOLDYREFF W. N. Influence of roentgen rays upon gastric secretion. *Amer J Roentgenol* 19 (1928) 61.
- CONRAD R. A. Dose dependence and sequential changes in mouse small intestinal weight induced by ionising radiation. *Proc Soc exp Biol* 86 (1954) 664.
- Some effect of ionising radiation in physiology of gastro-intestinal tract. *Review in Radiat Res* 5 (1956) 167.
- CORREIA J. P., COELHO C. S., GODINHO F. et coll. Use of labelled triolein and oleic acid in study of intestinal absorption. *Amer J dig Dis* 8 (1963) 649.
- GOODRICH J. A. and HICKMAN B. T. Oleic acid ¹⁸¹I intestinal absorption in pelvic cobalt 60 irradiation. *Amer J Roentgenol* 87 (1962) 69.
- CORDON H. S. J. Exudative enteropathy. *Lancet* 1959 I p. 325.
- COUGH K. R., READ A. E. and NAICH J. M. Intestinal reticulosis as a complication of idiopathic steatorrhea. *Gut* 3 (1962) 232.
- GRAHAM J. B. and VILLALBA R. J. Damage to the small intestine by radiotherapy. *Surg Gynec Obstet* 116 (1963) 665.
- HALLS J. M. Radiation damage to the small intestine. *Clin Radiol* 16 (1965) 172.
- ISLEY J. K., SHARPE K. W., BAYLIN G. J. and SANDERS A. P. An evaluation of the radioactive fecal fat analysis. *Amer J Roentgenol* 89 (1963) 797.
- PALMER W. L. and TEMPLETON F. The effect of radiation therapy on gastric secretion. *J Amer med Ass* 112 (1939) 1429.
- QUASTLER H. The nature of intestinal radiation death. *Radiat Res* 4 (1956) 303.
- and ZICKER M. The hierarchy of modes of radiation death in specifically protected mice. *Radiat Res* 10 (1959) 402.

- BRNSTD J P M, LAMERTON L F and SIMPSON S M Effects of dose rate and protraction. A symposium II Adaptation to continuous irradiation. Observation on rat intestine. *Brit J Radiol* 32 (1959) 501
- RAMOT B, SHAIKH N and RUBIN J J Malabsorption syndrome in lymphoma of small intestine. *Israel J med Sci* 1 (1965) 221
- REEVES R J, CAVANAUGH, SHARPE K W et coll Fat absorption studies and small bowel X ray studies in patients undergoing ^{60}Co teletherapy and/or radium application. *Amer J Roentgenol* 94 (1965) 848
- SANDERS A P, ISLEY J K et coll Fat absorption from the human gastro intestinal tract in patients undergoing radiation therapy. *Radiology* 73 (1959) 398
- — SHARPE K W et coll Fat absorption from human gastro-intestinal tract in patients undergoing teletherapy. *Amer J Roentgenol* 89 (1963) 122
- REITH W S, WILLIAMS E S and THOMAS M J The ^{131}I triolein fat absorption test. *Lancet* 1961 II p 1229
- RICAETS W E, PALMER W L, HIRSNER J H and HAMANN A Radiation therapy in peptic ulcer. An analysis of results. *Gastroenterology* 2 (1918), 789
- ROSEN I B and SHAPIRO B J Radiation enteropathy of the small bowel. *Canad med Ass J* 91 (1964) 681
- SANDERS A P, ISLEY J K, SHARPE K et coll Radioiodine recovery in feces following ^{131}I labelled fat test meal. *Amer J Roentgenol* 75 (1956) 386
- SCHILLING R F Intrinsic factor studies II The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B12. *J Lab clin Med* 42 (1963) 860
- SIRACKLEN F Reticulosis of the small bowel as a late complication of idiopathic steatorrhea. *Proc roy Soc Med* 56 (1963) 167
- SULLIVAN M F Polyvinylpyrrolidone labelled ^{131}I as an agent for the diagnosis of radiation injuries in rats. *Int J Radiat Biol* 2 (1960) 393
- WERNICK G Investigation of the effect of fractionated regimes of irradiation in normal tissues. *Brit J Radiol* 39 (1966) 272
- CREAMER H and SHORTER R G Recovery of the intestinal mucosa in the rat after X irradiation of the exteriorised intestine. *Radiat Res* 27 (1966) 264
- WILSON C W Cell survival data and the irradiation response of some normal tissues. *Radiology* 83 (1964) 120
- WOOD I J, RALSTON M and KURRIE G R Irradiation injury to the gastro intestinal tract. clinical features, management and pathogenesis. *Aust Ann Med* 12 (1963) 113

AUTOPSY FINDINGS IN LUNG CANCER TREATED WITH MEGAVOLTAGE RADIOTHERAPY

by

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The many advantages of megavoltage therapy have led to its increasing use during the last decade in radiotherapy of inoperable pulmonary carcinoma. The clinical experience obtained so far has not been very favourable, however. For instance, GUTTMANN (1958) achieved a one year survival rate of 33 per cent and a two-year survival rate of 9 per cent. Many other authors (HAAS *et coll.* 1957, KUTZ 1958, COCCHI 1961, 1964, BELING & ERNHORN 1965, HOLSTI 1965, 1967a, DEELEY 1967) have presented survival rates in roughly the same range. GUTTMANN (1964) reported slightly better results with megavoltage therapy after exploratory thoracotomy, although WATSON (1956) was considerably more pessimistic.

There are fairly few studies of the effects of megavoltage therapy on carcinoma of the lung based on autopsy materials. Five of WATSON'S (1956) cases were examined post mortem, and all of them had residual primary malignancy. GUTTMANN (1958) established three complete local cures (16 per cent) in an autopsy material of 19 cases. Four cures were claimed by HAAS *et coll.* (1957) following autopsies performed in seven cases. BELING & ERNHORN (1965) stated that autopsies revealed malignant tissue at the primary site in 48 of their 50 cases.

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The purpose of the present study was to establish from an autopsy material whether megavoltage therapy in the conventional dosage is capable of destroying primary lung carcinoma. In addition, special attention was paid to the cause of death in such cases.

Material and Methods The material comprised 67 histologically verified cases of inoperable carcinoma of the lung treated during the period 1963–1967 by megavoltage therapy and examined by autopsy 2 months to 4 years and 1 month (average 9 months) later. A total of about 1 400 cases of pulmonary carcinoma were treated at the clinic during the period. The histologic type was verified prior to treatment by biopsy in connection with bronchoscopy, tumour puncture, mediastinoscopy, scalenus biopsy or thoracotomy. Together with roentgenography these methods were used also to determine the size and localization of the growth.

Eight cases had metastases in the lymph nodes of the supraclavicular fossa or the neck, eighteen in the mediastinum, and three elsewhere (brain, liver) at the beginning of therapy. Of those treated, forty five were regarded as inoperable because of the size, central site, or metastases and five on account of the general condition (poor respiratory function, other lung conditions, cardiac disease). Nine cases were considered to be inoperable after exploratory thoracotomy, and in eight cases partial resection of the tumour was performed.

Forty six cases were treated with 33 MeV photons and twenty one with a 3 000 curie ^{60}Co unit. The commonest field size was 6 to 10 cm \times 10 to 12 cm. Mostly, 2 fields were used in photon therapy and 3 or 4 fields in ^{60}Co therapy.

The tumour dosage ranged from 4 000 to 7 000 rad over 5 to 10 weeks but was usually 4 500 to 5 500 rad over 5 to 8 weeks. Individual treatment planning was the rule, the aim in all treatments being to achieve a homogeneous dose distribution in the treatment volume. Thirty eight cases were treated with split course therapy (Holsti 1966, 1967b) and twenty nine cases continuously. The total tumour dose in the former was roughly 10 per cent higher than in the continuous treatment (Holsti 1967b). The treatment was repeatedly interrupted because of e.g. poor general condition, pyrexia, inflammation and anemia. In seven cases, complicating factors in three cases prolonged the treatment time to between 114 and 133 days. Therapy had to be discontinued in seven cases at 2 000 to 3 000 rad on account of the general condition. Sixty cases received the planned therapeutic dose.

The whole material of 67 cases was histologically distributed as follows: squamous cell carcinoma in 29, anaplastic carcinoma in 16, small cell carcinoma in 17, undifferentiated carcinoma in 3, and adenocarcinoma in 2 cases.

The mean survival time in the series was nine months. Forty four of the total series died of carcinoma or metastases, and twenty three from other causes (nine

Table 1

No carcinoma tissue at primary tumour site

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	6	1	7
Anaplastic carcinoma	2	—	2
Small cell carcinoma	4	2	6
Unclassified carcinoma	1	1	2
Adenocarcinoma	1	—	1
Total	14	4	18

Table 2

Islets of carcinoma cells in the fibrotic area at the site of the primary tumour

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	1	3	4
Anaplastic carcinoma	1	4	5
Small cell carcinoma	2	3	5
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	4	10	14

from pneumonitis eight from cardiac failure and four from a pulmonary embolus (one patient committed suicide and one died in an accident)

Results

The findings have been divided into four groups according to the type of primary growth at autopsy: (1) no carcinomatous tissue evident; (2) no definite malignancy macroscopically but microscopically fibrosis with obvious islets of carcinoma cells; (3) necrotic areas with malignant infiltration; and (4) viable malignant tissue in the treatment area.

1 *No carcinomatous tissue* Eighteen cases of the total series ($18/60=30$ per cent) had no carcinomatous tissue in the treatment area either macro- or microscopically. The distribution of the cases in this group by the histologic appearance appears in Table 1.

Partial resection of the growth was performed in six and exploratory thoracotomy in two of these eighteen cases. The tumour size in this group prior to

Table 3

Necrotic area with carcinomatous tissue (brackets = treatment not completed)

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	3	2 (1)	5
Anaplastic carcinoma	1	2 (1)	3
Small cell carcinoma	1 (1)	—	1
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	5	4	9

Table 4

Viable tumour tissue in the treatment area (brackets = treatment not completed)

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	7	6 (2)	13
Anaplastic carcinoma	3	3 (1)	6
Small cell carcinoma	3	2 (1)	5
Unclassified carcinoma	1	—	1
Adenocarcinoma	1	—	1
Total	15	11	26

treatment was 3 to 8 cm in diameter, usually 4 to 7 cm, the tumour dose was 4 800 to 6 250 rad. Fourteen (78 per cent) cases of this group were treated by the split course method and four received the entire course of irradiation as continuous therapy. No cytostatics were used. The pre-planned treatment scheme was fulfilled in all the cases and there were no complications. The condition of these eighteen cases appeared to be distinctly improved at the roentgenologic control performed after the termination of therapy. Eight patients died from distant metastases, and ten of some other cause, such as pneumonia, cardiac failure or pulmonary embolus.

2 Fibrosis with islets of carcinoma cells The fourteen (14/60=23 per cent) cases in this group are recorded histologically in Table 2.

Partial resection of the tumour was performed in one and exploratory thoracotomy in another of these cases. The growth was 4 to 8 cm in diameter and the dosage 4 700 to 7 000 rad. Cytostatics were also administered in three cases. Four of the cases were treated by the split course method and ten received continuous irradiation. The treatment was completed according to the therapeutic

Table 5

Localization of the metastases established at autopsy of 56 cases

Lymph nodes (including mediastinal and paratracheal lymph nodes)	34
Liver	30
Adrenals	27
Brain	22
Kidneys	20
Pancreas	19
Skeleton	16
Lungs	14
Abdominal cavity	9
Thyroid gland	7
Other	18

scheme in twelve cases and in the other two was interrupted because of complications (fever, anemia, etc). The condition in twelve cases was improved roentgenologically at the end of therapy while in two cases no change was observed. The cause of death was distant metastases in eleven cases and other conditions in three cases.

3 Necrotic areas containing carcinomatous tissue. The group comprised nine cases. Treatment had to be discontinued in three, leaving only six (6/60=10 per cent) cases that received the planned dosage. The distribution of the cases histologically appears in Table 3.

Three cases were subjected to exploratory thoracotomy. The average diameter of the mass in this group was 6 to 9 cm, the radiation dosage being 4,000 to 5,900 rad. In only three cases was it possible to complete the therapeutic course according to schedule. Six cases had complications (e.g., anemia, fever) necessitating interruption in the therapy. Five cases were managed by the split-course method and four cases received continuous treatment. Four cases were given cytostatics in addition to radiotherapy. Two cases were improved roentgenologically after the termination of the therapy and in the remaining seven cases there was no definite change. Seven patients died from distant metastases and two from other causes. It is possible that the treatment volume was too small in two of the cases in this group.

4 Viable carcinoma tissue in the treatment area. The fourth group comprised 26 cases. Treatment had to be discontinued in four of them and thus viable carcinomatous tissue was demonstrable both macroscopically and microscopically in the treatment area in 22/60 cases, i.e., 37 per cent of those that received roughly the planned dosage. The histologic distribution is given in Table 4.

Table 6

Correlation between autopsy findings and radiation dose

	> 4 000 rad	> 5 000 rad	> 6 000 rad	Total
No carcinoma	8	8	2	18
Fibrosis	3	7	4	14
Necrosis	4	2	—	■
Viable carcinoma	6	11	5	22
Total	21	28	11	60

Exploratory thoracotomy was performed in three cases and partial resection of the tumour in one case. The growth was 6 to 9 cm in diameter and the dosage 4 000 to 6 000 rad. The split course technique was employed in fifteen cases and continuous radiotherapy in eleven cases. The therapy was completed according to schedule in only thirteen cases, and in the other thirteen complications (anaemia, fever, etc) interfered and in three of the latter cases prolonged the treatment time to 114—133 days.

Röntgenography at the termination of the primary treatment indicated improvement in seventeen and no obvious change in nine cases. A recurrence was observed roentgenologically in four cases 3 to 6 months after the primary therapy. The treatment fields may have been too small or the tumour may not have been precisely localized in these cases. One of the cases was treated with cobalt 60 therapy with the breathing of pure oxygen 20 minutes prior to therapy and during it. The fractionation was 600 rad twice a week, total dosage 4 700 rad, 54 days (split course technique).

Nineteen of the patients in this group died of the primary disease or distant metastases. Seven patients died from other causes.

Metastases were demonstrated in fifty six cases of the total autopsy material; the locations appear in Table 5. The ratio between the autopsy finding and the radiation dose is given in Table 6.

Discussion

The prognosis of inoperable carcinoma of the lung treated with radiotherapy is generally considered to be poor (e.g. GUTTMANN 1955, 1958, 1961, HAAS *et al.* 1957, KUTZ 1958, COCCHI 1961, 1964, BEIING & LINHORN 1965, HOLSTI 1965, 1967a). Some authors are completely pessimistic about the treatment (WATSON 1956). Almost invariably the starting point for radiotherapy is unfavourable. The tumour is often of considerable size, as well as infiltrating, and thus inoperable. The subjects are frequently elderly in poor condition and anemic,

Table 7

Autopsy findings and histologic features in the split-course group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adeno- carcinoma	Total
No carcinoma tissue	6	2	4	1	1	14
Fibrosis + carcinoma	1	1	2	—	—	4
Necrosis + carcinoma	3	1	1	—	—	5
Visible carcinoma tissue	7	3	3	1	1	15
Metastases	12/(17)	5/(7)	10/(10)	1/(2)	1/(2)	29/(38)

Table 8

Autopsy findings and histologic features in the continuous therapy group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adeno- carcinoma	Total
No carcinoma tissue	1	—	2	1	—	4
Fibrosis + carcinoma	3	4	3	—	—	10
Necrosis + carcinoma	2	2	—	—	—	4
Visible carcinoma tissue	6	3	2	—	—	11
Metastases	11/(12)	8/(9)	7/(7)	1/(1)	—	27/(29)

with infection as a prominent feature. In addition metastases are often already present. However, in the present material, which was of a wholly random character, the carcinoma had actually disappeared microscopically in eighteen (30 per cent) of the cases that received the full planned therapy of at least 4,800 rad. There were no complicating factors in these cases. Fourteen (78 per cent) of the cases were treated by the split course technique, which suggests that the method has definite advantages. Bearing in mind that there was no true random selection of cases for split course or continuous therapy in this series, comparison of the two methods (Tables 7 and 8) indicate that the primary tumour disappeared completely in 37 per cent of the cases treated by the former and in only 14 per cent of those treated by the latter method.

Both microscopic and microscopic regression frequently occurs during the interval of the split course therapy (Holsti 1967c), which may contribute to the good end result. Metastases were encountered in 76 per cent of the cases treated by the split course technique and in 93 per cent of those given continuous therapy.

The distribution of the metastases in the total material concurred on the

whole with that reported by ROSENBLATT & LISA (1956). All the cases with complete loss of malignant tissue had received over 4 800 rad. Fourteen cases (23 per cent) had islets of carcinoma cells in the fibrotic areas. Recurrence might well arise from such residual foci, as has been stressed in radiobiologic studies based on cell survival observations (FOWLER 1966). In those groups in which viable carcinomatous tissue, or necrotic areas with islets of malignancy, were found at autopsy in the therapeutic area, over half the number of cases (67 per cent in group 3, 50 per cent in group 4) had complications during therapy. This prevented the realisation of the radiotherapeutic plan and thus impaired the end results.

The treatment had to be interrupted in seven cases by the time the patients had received 2 000 to 3 000 rad. All still showed evidence of malignancy, in three of the cases in addition to necrotic tissue. The dose administered had obviously been incapable of destroying the tumour tissue. Prolongation of the treatment time on account of protracted or recurrent complications, such as pyrexia or anemia, considerably hinders the chances of recovery.

However, it was only in a few rare cases in which the therapeutic programme could be completed without noteworthy complicating factors (at a dosage of 4 000 to 6 000 rad) that viable carcinomatous tissue was demonstrated. Only the individual radiosensitivity of the tumour can properly account for this, an important factor being the anoxic cells. THOMLINSON & GRAY (1955) in pulmonary carcinoma in human subjects, regularly observed small necrotic anoxic areas more than 180 μ from the nearest capillary. The proportion of anoxic cells in tumours is extremely important in relation to the radiation dosage needed for radical treatment and can make all the difference between success and failure (FOWLER et al. 1963). Viewed against this background, it is perhaps not always most purposeful to aim at homogeneous dose distribution in radiation therapy. Anoxic areas need larger doses than well oxygenated areas. The roentgenologic appearances were improved in 18/18 cases in group 1, in 12/14 cases in group 2, in 2/9 cases in group 3 and in 17/26 cases in group 4. These observations suggest that roentgenologic evidence of decrease or disappearance of the growth is an indication that local control of tumour is possible.

Obviously, the smaller the tumour, the greater are the chances of success. This is borne out too by the fact that the fully healed cases included six that had been subjected to palliative surgery. But even if the tumour is destroyed completely, latent or subsequent metastases may impair the end result so that the final clinical results deteriorate as the patient succumbs to the metastases. In any event it would appear that it is possible under favourable conditions to destroy the primary focus of pulmonary carcinoma by megavoltage therapy at a dosage of 4 800 to 6 000 rad.

In summary two-thirds of the patients in the present material died of the primary growth or metastases. In eighteen cases i.e. 30 per cent the tumour was sterilized by radiotherapy and the patients died from other diseases though eight of these even had distant metastases. The study confirms the view that the greatest problem in the treatment of carcinoma of the lung is its readiness to form metastases. The individual radiosensitivity of the tumours (e.g. the number of anoxic cells) obviously also play an important role.

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SUMMARY

The autopsy findings in 67 cases of inoperable carcinoma of the lung treated with megavoltage therapy were analysed to determine whether the primary tumour had been destroyed. Seventy-eight per cent of the cases of complete cure had been treated by the split course technique. Forty-four of the total of 67 patients i.e. 66 per cent died from the original condition or metastases and twenty-three (34 per cent) from other causes.

ZUSAMMENFASSUNG

Die Autopsiebefunde in 67 Fällen von nicht operierbaren Lungenkarzinomen wurden analysiert um festzustellen ob der Primärtumor vollständig durch die Megavolt Röntgenbestrahlung zerstört wurde. In 78% der Fälle die mit unterbrochener Serienbestrahlung behandelt wurden konnte eine vollständige Heilung erreicht werden. Primärtumore oder Metastasen verursachten den Tod in 66% (44 Patienten) während 34% (23 Patienten) infolge anderer Ursachen starben.

RÉSUMÉ

Les auteurs ont étudié les résultats d'autopsie de 67 cas de cancer du poumon inopérable traités par radiothérapie à megavoltage pour savoir si la tumeur primitive avait été détruite. Soixante dix huit pour cent des cas de guérison complète avaient été traités par la technique de fractionnement du traitement (split course). Quarante quatre des malades sur un total de 67 c'est à dire 66 pour cent sont morts du cancer primitif ou de métastases et 23 (34 pour cent) ont morts d'autres affections.

REFERENCES

- BRUND U. and FINNORS J. Radiotherapy of carcinoma of the lung. *Acta radiol. Ther. Phys. Biol.* 3 (1965) 281.
 COCCU L. Die Strahlentherapie der Bronchustumoren. *Zürcher Erfahrungen mit dem 31 MeV Betatron 1957—1959*. *Fortschr. Röntgenstr.* 94 (1961) 792.
 — Was erreicht die Strahlentherapie beim Bronchuscarcinom. *Radiol. clin.* 33 (1964) 93.

- DRILEY F. J. The treatment of carcinoma of the bronchus. Review article *Brit J Radiol* 40 (1967) 801.
- LOWIEF J. I. Radiation biology as applied to radiotherapy. Current topics in radiation research Vol II, p. 303. North Holland Publ. Co. Amsterdam 1966.
- MORCAN R. L. and WOOD C. A. P. Pre therapeutic experiments with the fast neutron beam from the Medical Research Council cyclotron. I. The biological and physical advantages and problems of neutron therapy *Brit J Radiol* 36 (1963) 77.
- GUTTMANN R. J. Two million volt irradiation therapy for inoperable carcinoma of lung. *Cancer* 8 (1955) 1254.
- Experiences in the treatment of inoperable carcinoma of the lung with 2 MeV and cobalt 60 irradiation. *Amer J Roentgenol* 79 (1958) 505.
- Intensive cobalt 60 teletherapy of lung cancer. *Radiology* 71 (1958) 327.
- Comparison of three different methods of external irradiation and their results in the treatment of the inoperable carcinoma of the lung. *Radiology* 76 (1961) 83.
- Results of radiotherapy in cancer of the lung classified as inoperable at exploratory thoracotomy. *Cancer* 17 (1961) 37.
- HAAS I. I., HARVEY R. A. and MELCHER F. C. Radiotherapeutic experiences with inoperable lung carcinoma. *Cancer* 10 (1957) 280.
- HOLSTI L. R. Cobalt 60 therapy of carcinoma of the lung. *Ann Chir Gynaec Fenn* 54 (1965) 261.
- Split course megavoltage radiotherapy. One year follow up. *Brit J Radiol* 39 (1966) 332.
- (a) Roentgen and tele cobalt therapy of cancer of the lung. *Acta radiol Ther Phys Biol* 6 (1967), 65.
- (b) Split course radiotherapy of cancer. *Acta radiol Ther Phys Biol* 6 (1967) 313.
- (c) Clinical experience of split course radiotherapy. Paper read at IX Interamer. Congress of Radiology, Punta del Este, Uruguay, December 6–12 1967.
- KUTZ F. R. Intensive cobalt 60 teletherapy of lung cancer. *Radiology* 71 (1958) 327.
- ROSENBLATT M. B. and LISA J. R. *Cancer of the lung. Pathology, diagnosis and treatment*. Oxford University Press, New York 1956.
- THOMLINSON R. H. and GRAY L. H. The histological structure of some human lung cancers and the possible implications for radiotherapy. *Brit J Cancer* 9 (1955) 539.
- WATSON I. A. Supervoltage roentgen therapy in cancer of the lung. *Amer J Roentgenol* 75 (1956) 525.

SOME EFFECTS OF DATA ERROR IN THE ANALYSIS OF RADIOTRACER DATA

by

J MYHILL

Radioactive tracers have been used extensively to study some aspects of biological function in man. The results of a radiotracer study may often be a series of measurements of radioactivity extending over an interval of time after administration of the radioisotope. It is sometimes appropriate to represent the aspects which are under investigation by a simplified compartmental model and to fit the solution function of the model to the experimental data points in order to estimate the model parameters. If the system is in a steady state then it has been previously shown that the behaviour of labelled substances can be represented by linear differential equations (SHEPPARD & HOLSEHOEDER 1951; BERMAN & SCHOENFELD 1956) and that the solution for the activity versus time curve in each compartment consists of a sum of exponentials

$$f(t) = \sum_{i=1}^n A_i e^{-\lambda_i t}$$

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How the errors and omissions in the data affect the estimation of the rate constants, λ_i , and the amplitudes, N_i , and through them the estimation of the transfer rates and compartment sizes, has recently become a subject of study (MYHILL, WADSWORTH & BROWNELL 1965, MYHILL 1965, 1966, 1967 a c)

The collection of data is usually terminated for some experimental reason. The radioactivity may become too low to count accurately, the patient may become unavailable for study, or the radioactive label may become detached from its compound. This data truncation, together with the experimental error in each measured data point and the fewness of points, creates uncertainty in the values of the model parameters. This is the case even where a valid, unequivocal model of the system is assured.

Method of error analysis

1 *Computer simulation of data* Data points were simulated on a high speed digital computer (English Electric KDF 9) using the equation for $f(t)$ and some random number generators. The details of the simulation have been previously described (MYHILL 1968).

The situations where λ_1/λ_2 equals 10, 6, 4 and 2 were studied, the cases where the rate constants λ_i are closer to equality being the more difficult. If λ_1/λ_2 is less than about four, some methods of analysis become less effective (BROWNELL & CALLAHAN 1963) or are subject to large bias (MYHILL, WADSWORTH & BROWNELL 1965). The ratio N_1/N_2 was set equal to 10, 6, 4, 2 or 1. The special case of $N_1/N_2 = \lambda_1/\lambda_2$ has been previously reported (MYHILL 1967c). The simulated data were terminated when the value of the last data point was 5 % of the value of the initial point. This corresponds to a situation often observed in reports of experiments and is a more difficult case to analyse than if the data were further extended in time (i.e. so that the value of the last data point was less). In an endeavour to approximate to types of data seen in the literature, the cases of 31 and 11 data points equally spaced over the time interval of data collection, or else equally spaced in log time (more points taken over the early portions of the data), were investigated. Random error with a constant per cent standard deviation was simulated at each point. The statistical distribution of the error was normal since it had been shown previously that the form of the statistical distribution of the error was of minor importance (MYHILL 1967, 1968) and the magnitude of the standard deviation of error in a data point in any one set of data was varied from 0.5 % to 10 % between sets. The type of data simulated is shown in Figs 1 and 2 (continuous curves shown there without random errors added).

Table 1

Maximum amount of error in the data that allows convergence

Ratio of rate constants λ_2/λ_1	Ratio of amplitudes A_2/A_1	Number of data points			
		11		31	
		Equal spacing	Log equal spacing	Equal spacing	Log-equal spacing
10/1	6/1	10	10	10	10
10/1	4/1	10	10	10	10
10/1	2/1	10	10	10	10
10/1	1/1	*	*	10	10
6/1	10/1	3	1	6	3
6/1	4/1	10	7	10	10
6/1	2/1	10	10	10	10
6/1	1/1	*	*	9	10
4/1	10/1	1	0.5	2	2
4/1	6/1	4	1	6	3
4/1	2/1	8	4	10	8
4/1	1/1	*	*	10	8
2/1	10/1	*	*	0.5	**
2/1	6/1	*	*	0.5	0.5
2/1	4/1	*	*	1	0.5
2/1	1/1	*	*	2	1

The error entered in the table is the percentage standard deviation at a data point. The error was normally distributed and of constant percent standard deviation throughout a set of data. The data were terminated such that the value of the last data point was 5% of the value of the first data point. The maximum percent data error employed was 10.

This combination of conditions was not simulated.

For convergence with these simple methods require an error less than 0.5.

2 Numerical analysis of simulated data The function, $f(t)$ was fitted to each set of data using a valid non linear least squares method. The estimated values of the λ_i , A_i and their estimated standard deviations deduced from the variance covariance matrix of each fit were obtained. Each set of data was simulated fifty times (with everything the same except the random numbers employed to simulate the error) and analysed fifty times. By this means the variability and bias of both the estimates of the parameters and the estimates of their standard deviations were studied.

The computer programmes were written in Algol and run on an English Electric KDF 9 computer. When this work was commenced the University

Table 2

Average standard deviations of λ_1 as per cent of the true λ_1 — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_1/λ_2	Ratio of amplitudes A_1/A_2	Error in data	Number of data points							
			11				31			
			Equal spacing		Log equal spacing		Equal spacing		Log equal spacing	
			λ_1	λ_2	λ_1	λ_2	λ_1	λ_2	λ_1	λ_2
10/1	6/1	2 %	2.6	4.8	2.9	6.5	1.8	3.1	1.8	5.1
		5 %	6.5	12.1	7.8	17.3	4.5	7.8	4.5	12.7
		10 %	13.2	23.0	15.2	36.6	9.7	15.9	9.3	26.9
10/1	4/1	2 %	3.1	2.7	3.1	3.6	2.1	1.8	2.0	2.9
		5 %	7.6	6.9	8.2	9.6	5.3	4.4	4.9	7.4
		10 %	15.4	12.9	15.9	18.5	11.6	8.9	10.3	15.4
10/1	2/1	2 %	5.0	1.6	4.8	2.3	3.2	1.0	2.8	1.7
		5 %	12.4	4.1	11.9	5.8	8.3	2.5	6.9	4.2
		10 %	37.8	7.7	23.6	11.1	16.7	5.1	14.5	9.0
10/1	1/1	2 %	*	*	*	*	5.5	0.7	4.5	1.2
		5 %	*	*	*	*	14.4	1.9	11.1	3.1
		10 %	*	*	*	*	34.3	3.9	23.4	6.7
6/1	10/1	1	*	*	5.4	62.7	*	*	*	*
		2 %	4.8	36.5	**	**	3.2	25.5	3.7	36.6
		5 %	**	**	**	**	7.8	67.3	**	**
6/1	4/1	1 %	*	*	*	*	*	*	1.3	2.6
		5 %	8.7	13.2	12.7	23.1	6.0	8.5	6.7	13.3
		10 %	18.4	25.3	**	**	13.5	17.3	13.0	26.7
6/1	2/1	2 %	4.8	2.4	5.2	3.2	3.2	1.6	3.3	3.5
		5 %	11.6	6.2	13.7	8.6	8.1	3.8	8.1	6.3
		10 %	22.5	11.7	28.0	20.1	*	*	17.2	13.6
6/1	1/1	2 %	*	*	*	*	5.1	10.2	5.0	1.7
		5 %	*	*	*	*	13.1	2.6	12.3	4.4
		10 %	*	*	*	*	**	**	26.6	9.5
4/1	10/1	0.5	1.8	14.5	4.8	54.3	*	*	1.5	14.1
		1	3.5	30.3	**	**	2.5	20.1	2.9	27.8
		2	**	**	**	**	4.8	41.7	6.2	38.1
4/1	6/1	1	2.9	11.6	6.7	37.0	2.1	8.1	2.4	11.3
		2	5.9	24.5	**	**	4.0	16.6	4.8	22.3
		5	**	**	**	**	10.6	40.0	**	**
4/1	2/1	2	5.9	4.3	8.4	7.7	4.0	3.0	4.5	4.5
		5	14.3	10.7	**	**	10.4	7.6	11.6	11.7
		10	**	**	**	**	22.8	17.1	**	**
4/1	1/1	2	*	*	*	*	5.7	1.8	6.2	2.7
		5	*	*	*	*	14.4	4.7	15.2	7.0
		10 %	*	*	*	*	33.8	12.5	**	**
2/1	10/1	0.5 %	**	**	**	**	4.6	28.8	**	**
2/1	6/1	0.5	**	**	**	**	3.5	17.4	4.7	22.2
2/1	4/1	0.5 %	**	**	**	**	3.4	11.0	4.4	14.1
		1	**	**	**	**	7.2	22.0	**	**
2/1	1/1	0.5 %	*	*	*	*	4.2	2.7	5.1	3.8
		1 %	*	*	*	*	8.3	6.1	9.9	7.8
		2 %	*	*	*	*	16.8	12.1	**	**

* Calculated, ** Computed, ** Obtained

Table 3

Average standard deviations of λ_1 as per cent of true λ_1 — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ/λ	Ratio of amplitudes λ/λ	Error in data	Number of data points							
			11				31			
			Equal spacing λ		Log equal spacing λ		Equal spacing λ		Log equal spacing λ	
10/1	6/1	2	22	39	11	59	16	25	08	40
		5	52	99	31	155	38	63	19	101
		10	104	190	60	306	82	132	40	208
10/1	4/1	2	24	27	12	41	19	17	08	28
		5	60	69	34	104	47	44	21	68
		10	118	130	65	202	101	89	44	143
10/1	2/1	2	31	20	18	31	26	12	11	20
		5	77	53	48	79	64	32	28	49
		10	147	100	92	153	130	64	60	103
10/1	1/1	2		*		*	37	11	19	17
		5				*	93	28	46	41
		10					199	59	96	88
6/1	10/1	1		*	48	491				*
		2	29	335			19	226	30	312
		5		**		**	45	525		**
1/1	4/1	1		*					07	30
		5	57	150	63	264	39	99	37	151
		10	117	287			84	203	69	281
1/1	2/1	2	31	34	26	51	22	22	13	35
		5	76	88	68	134	55	56	44	86
		10	153	167	142	282			90	179
1/1	1/1	2		*			33	17	27	27
		5		*			84	44	66	66
		10				*		*	143	142
4/1	10/1	0.5	17	190	59	598			18	175
		1	33	303			23	263	34	351
		2				*	44	491	72	734
4/1	6/1	1	24	162	69	425	16	110	25	151
		2	45	311			30	215	48	293
		5					75	526		*
4/1	2/1	2	39	75	65	135	25	51	36	76
		5	93	176			63	120	90	186
		10				*	132	251		**
4/1	1/1	2					35	32	48	50
		5					93	88	122	125
		10					203	174		
2/1	10/1	0.5					115	116		*
2/1	1/1	0.5				*	79	485	113	679
2/1	4/1	0.5				*	75	309	103	412
1	1/1	1				*	146	603		
		0.5					85	88	118	119
		1					175	182	223	225
		2					307	320		
Total number of conditions with no correlation										

Table 2

Average standard deviations of λ_1 as per cent of the true λ_1 — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_1/λ_2	Ratio of amplitudes N_1/N_2	Error in data	Number of data points							
			11				31			
			Equal spacing λ_1 λ_2		Log equal spacing λ_1 λ_2		Equal spacing λ_1 λ_2		Log equal spacing λ_1 λ_2	
10/1	6/1	2 %	2.6	4.8	2.9	6.5	1.8	3.1	1.8	5.1
		5 %	6.5	12.1	7.8	17.3	4.5	7.8	4.5	12.7
		10 %	13.2	23.0	15.2	36.6	9.7	15.9	9.3	26.9
10/1	4/1	2 %	3.1	2.7	3.1	3.6	2.1	1.8	2.0	2.9
		5 %	7.6	6.9	8.2	9.6	5.3	4.4	4.9	7.4
		10 %	15.4	12.9	15.9	18.5	11.6	8.9	10.3	15.4
10/1	2/1	2 %	5.0	1.6	4.8	2.3	3.2	1.0	2.8	1.7
		5 %	12.4	4.1	11.9	5.8	8.3	2.5	6.9	4.2
		10 %	37.8	7.7	23.6	11.1	16.7	5.1	14.5	9.0
10/1	1/1	2 %	*	*	*	*	5.5	0.7	4.5	1.2
		5 %	*	*	*	*	14.4	1.9	11.1	3.1
		10 %	*	*	*	*	34.3	3.9	23.4	6.7
6/1	10/1	1 %	*	*	5.4	62.7	*	*	*	*
		2 %	4.8	36.5	**	**	3.2	25.5	3.7	36.6
		5 %	**	**	**	**	7.8	67.3	**	**
6/1	4/1	1 %	*	*	*	*	*	*	1.3	2.6
		5 %	8.7	13.2	12.7	23.1	6.0	8.5	6.7	13.3
		10 %	18.4	25.3	**	**	13.5	17.3	13.0	26.7
6/1	2/1	2 %	4.8	2.4	5.2	3.2	3.2	1.6	3.3	3.5
		5 %	11.6	6.2	13.7	8.6	8.1	3.8	8.1	6.3
		10 %	22.5	11.7	28.0	20.1	*	*	17.2	13.6
6/1	1/1	2 %	*	*	*	*	5.1	10.2	5.0	1.7
		5 %	*	*	*	*	13.1	2.6	12.3	4.4
		10 %	*	*	*	*	**	**	26.6	9.5
4/1	10/1	0.5 %	1.8	14.5	4.8	54.3	*	*	1.5	14.1
		1 %	3.5	30.3	**	**	2.5	20.1	2.9	27.8
		2 %	**	**	**	**	4.8	41.7	6.2	58.6
4/1	6/1	1 %	2.9	11.6	6.7	37.0	2.1	8.1	2.4	11.3
		2 %	5.9	24.5	**	**	4.0	16.6	4.8	22.3
		5 %	**	**	**	**	10.6	40.0	**	**
4/1	2/1	2 %	5.9	4.3	8.4	7.5	4.0	3.0	4.5	4.5
		5 %	14.3	10.7	**	**	10.4	7.6	11.6	11.7
		10 %	**	**	**	**	22.8	17.1	**	**
4/1	1/1	2 %	*	*	*	*	5.7	1.8	6.2	2.7
		5 %	*	*	*	*	14.4	4.7	15.2	7.0
		10 %	*	*	*	*	33.8	12.5	**	**
2/1	10/1	0.5 %	**	**	**	**	4.6	28.8	**	**
2/1	6/1	0.5 %	**	**	**	**	3.5	17.4	4.7	22.2
2/1	4/1	0.5 %	**	**	**	**	3.4	11.0	4.4	14.1
		1 %	**	**	**	**	7.2	22.0	**	**
2/1	1/1	0.5 %	*	*	*	*	4.2	2.7	5.1	3.8
		1 %	*	*	*	*	8.3	6.1	9.9	7.8
		2 %	*	*	*	*	16.8	12.1	**	**

* This combination of conditions was not simulated ** Convergence not obtained

Table 3

Average standard deviations of λ_1 as per cent of true λ_1 — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants k_1/k_2	Ratio of amplitudes A_1/A_2	Error in data	Number of data points							
			11				31			
			Equal spacing		Log-equal spacing		Equal spacing		Log-equal spacing	
			λ_1	λ_2	λ_1	λ_2	λ_1	λ_2	λ_1	λ_2
10/1	6/1	2	2.2	5.9	1.1	5.9	1.6	2.5	0.8	4.0
		5	5.2	9.9	3.1	15.5	3.8	6.3	1.9	10.1
		10	10.4	19.0	6.0	30.6	8.2	13.2	4.0	20.8
10/1	4/1	2	2.4	2.7	1.2	4.1	1.9	1.7	0.8	2.8
		5	6.0	6.9	3.4	10.4	4.7	4.4	2.1	6.8
		10	11.8	13.0	6.5	20.2	10.1	8.9	4.4	14.3
10/1	2/1	2	3.1	2.0	1.8	3.1	2.6	1.2	1.1	2.0
		5	7.7	5.3	4.8	7.9	6.4	3.2	2.8	4.9
		10	14.7	10.0	9.2	15.3	13.0	6.4	6.0	10.3
10/1	1/1	2	*	*	*	*	3.7	1.1	1.9	1.7
		5	*	*	*	*	9.3	2.8	4.6	4.1
		10	*	*	*	*	19.9	5.9	9.6	8.8
1/1	10/1	1	*	*	4.8	49.1	*	*	*	*
		2	2.9	35.5	*	*	1.9	22.6	3.0	31.2
		5	**	**	*	*	4.5	57.5	*	*
1/1	4/1	1	*	*	*	*	*	*	0.7	3.0
		5	5.7	15.0	6.3	26.4	3.9	9.9	3.7	15.1
		10	11.7	28.7	*	*	8.4	20.3	6.9	28.1
1/1	2/1	2	3.1	3.4	2.6	5.1	2.2	2.2	1.3	3.5
		5	7.6	8.8	6.8	13.4	5.5	5.6	4.4	8.6
		10	15.3	16.7	14.2	28.2	*	*	9.0	17.9
1/1	1/1	2	*	*	*	*	3.3	1.7	2.7	2.7
		5	*	*	*	*	8.4	4.4	6.6	6.6
		10	*	*	*	*	*	*	14.3	14.2
4/1	10/1	0.5	1.7	19.0	5.9	59.8	*	*	1.8	17.5
		1	3.3	36.3	*	*	2.3	26.3	3.4	35.1
		2	*	*	*	*	4.4	49.1	7.2	73.4
4/1	1/1	1	2.4	16.2	6.9	47.4	1.6	11.0	2.5	15.1
		2	4.5	31.1	*	*	3.0	21.5	4.8	29.3
		5	*	*	**	**	7.5	52.6	*	*
4/1	2/1	2	3.9	7.5	6.5	13.4	2.5	5.1	3.6	7.6
		5	9.3	17.6	*	*	6.3	12.6	9.0	18.6
		10	*	*	*	*	13.9	25.1	*	*
4/1	1/1	2	*	*	*	*	3.5	3.2	4.8	5.0
		5	*	*	*	*	9.3	8.8	12.2	12.5
		10	*	*	*	*	20.3	17.4	*	*
2/1	10/1	0.5	*	*	*	*	11.5	11.6	*	*
2/1	6/1	0.5	*	*	*	*	7.9	48.5	11.3	67.9
2/1	4/1	0.5	*	*	**	**	7.5	30.9	10.3	41.2
2/1	1/1	1	**	**	*	*	14.6	60.3	*	*
		1	*	*	*	*	8.5	8.8	11.8	11.9
		2	*	*	*	*	17.5	18.2	22.3	22.5
The only situation of one data point was not simulated							30.7	32.0	*	*

Convergence not obtained

of Sydney did not possess an IBM 7090, or a Fortran compiler, and thus none of the well known fitting programmes, e.g. BERMAN, SHAHIN & WEISS (1962) could be used

Results

1 Convergence of the iterations The maximum amount of error in the data that permitted convergence of this simple numerical technique was as shown in Table 1. In each case the true parameter values (used in generating the relevant data) were used as starting values for the iteration. From the point of view of starting values, these results thus represent the most favourable situation it is possible to achieve.

No special techniques were used to help the convergence. Each set of data was simulated fifty times, and a failure to converge for at least one set was regarded as meaning that convergence was not obtained for those data. In these regards the results are somewhat less favourable than might be obtained in practice.

Failure of convergence was judged to have occurred if, in the process of calculation, a number exceeded the machine limit ($\sim 10^{10}$) (this was almost always the case) or, rarely, if the change in parameter values was not less than 10^{-4} and the change in variance not less than 10^{-4} after twenty iterations. The parameter values were in the range 0.01 to 1.00.

2 Error in the λ_i as a function of error in data and number of data points Table 2 shows the average error (throughout this paper error means percentage error) in λ_1 and λ_2 as a function of magnitude of error in the data, and number of data points, for normally distributed error. One result is obvious: 31 points give a lower error than 11 points for the same data error.

The lesser rate constant, λ_2 , which largely determines the tail of the data, has more error than the greater constant, λ_1 , if $N_1/N_2 > 1$ and $\lambda_1/\lambda_2 \geq 4$, and if the data are spaced equally in log time. The same holds for equally spaced data except that if $\lambda_1/\lambda_2 = 10$ and $N_1/N_2 = 1$, then the error in λ_2 is the least. If $\lambda_1/\lambda_2 \geq 4$ and $N_1/N_2 \leq 2$, then the error in λ_2 is lower than in λ_1 , except that for $\lambda_1/\lambda_2 = 4$ and $N_1/N_2 = 2$, the errors are equal. For $\lambda_1/\lambda_2 = 2$, the error in λ_2 is lower for $N_1/N_2 = 1$ only. These statements apply to the studies with 31 points and the error referred to is the percentage error, as is always the case in this paper.

The same results were observed in studies with eleven points except that for data spaced equally in log time if $\lambda_1/\lambda_2 = 1$ and $N_1/N_2 = 2$, then the error in λ_2 is the lesser.

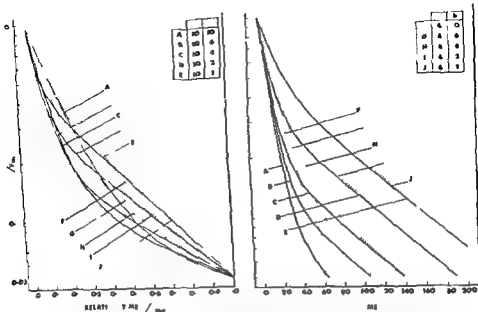


Fig. 1 Sums of two exponentials having rate constants of ratio 10 and 6. The amplitude ratios are 10, 6, 4, 2 and 1. A sum is terminated when it has declined to 5% of its initial value. Each curve is plotted twice: on the left both magnitude and time are normalised; on the right the magnitude alone is normalised.

The percent error in λ_1 was only sometimes lessened by employing log equal spacing of the data, while the percent error in λ_2 was always increased.

3. Error in λ_1 as a function of error in data and number of data points. The average errors in λ_1 and λ_2 as a function of magnitude of error in the data and number of data points for normally distributed error are shown in Table 3.

With 31 points and log equally spaced data the percent error in λ_2 is equal to that in λ_1 when $\lambda_1/\lambda_2 = 1$ irrespective of λ_1/λ_2 and is greater than that in λ_1 for all other values of λ_1/λ_2 . The same holds for 11 points.

For equally spaced data if $\lambda_1/\lambda_2 \geq \lambda_1/\lambda_2$ then the percent error in λ_2 is the greater. The errors are about equal for $\lambda_1/\lambda_2 = 10$ and $\lambda_1/\lambda_2 = 4$, $\lambda_1/\lambda_2 = 6$ and $\lambda_1/\lambda_2 = 2$, $\lambda_1/\lambda_2 = 4$ or 2 and $\lambda_1/\lambda_2 = 1$. For each of these values of λ_1/λ_2 , if λ_1/λ_2 exceeds the value quoted then the percent error in λ_2 is the greater; otherwise it is the lesser.

For log equal spacing the absolute errors in the λ_1 are approximately equal.

For $\lambda_1/\lambda_2 \geq 6$ the log equal spacing (i.e. crowding the points near the

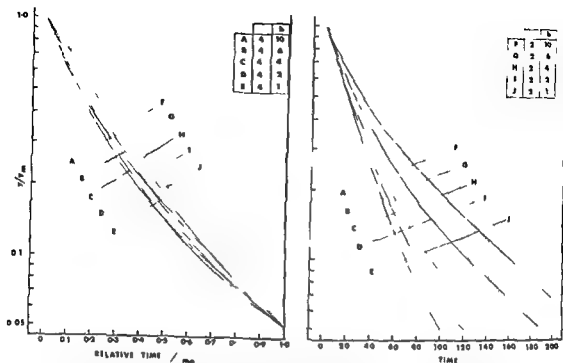


Fig. 2. Sums of two exponentials having rate constants of ratio 4 and 2. The amplitude ratios are $10/6 + 2$ and 1. A sum is terminated when it has declined to $1/5$ of its initial value. Each curve is plotted twice: on the left both magnitude and time are normalised; on the right the magnitude alone is normalised.

beginning of the data) always improved the per cent error in N_1 , over that obtained in equally spaced data. For $\lambda_1/\lambda_2 \leq 4$ the opposite was true.

Discussion

The tracer activity curve in any steady state two compartment open system can be described by a sum of two exponential terms. The relationships between the transfer rates and compartment sizes, on the one hand, and the rate constants (λ_i) and amplitudes (N_i), on the other hand, are expressible by simple algebraic equations. The form of the equations depends on the configuration of the system, and these equations can be used to transform information on the errors obtained in λ_i and N_i to information about the associated errors in the transfer rates and compartment sizes. By this means this error information can be applied to a range of biological problems, mainly tracer studies in biochemistry and physiology.

Within the conditions here investigated convergence is readily obtained by this simple numerical method if the ratio of λ_1 to λ_2 is not less than about

four For lower ratios (i.e. rate constants more nearly equal) a very good experiment is necessary that is, the standard deviation in each data point should be about 1 %. In practice since the best starting values for the iteration are of course unknown convergence may be difficult to obtain even when these requirements are satisfied However the employment of various techniques to help convergence and trial of various starting values would improve the situation over that shown in Table 1

For any desired error in λ_1 or λ_2 the allowable error in the data may be found from Tables 2 and 3 As the data error increases the parameter error increases proportionately For the same error in each point taking more points results in a smaller parameter error The variation of error in the λ_1 and λ_2 depends on the spacing of the data points and the ratios λ_1/λ_2 and λ_1/λ The parameter errors could be reduced by collecting data extending further in time as well as by lowering the error in each point or taking more points over the same time interval The present study, however was to examine the situation where for experimental reasons the data could not be extended further in time

The conclusions of this paper apply to any two compartment system from which data has been collected until $f(t) = qf(0)$, $q = 0.05$ in one of the compartments, and for which $\lambda_1 > \lambda_2$ implies $\lambda_1 \geq \lambda_2$ The results do not depend on the absolute magnitudes of the λ_1 or λ_2 In practice if q is larger then the analysis is more difficult the errors in λ_1 and λ_2 will be greater and the situation is worse in other respects If q is smaller, i.e. the data are sampled for a longer time the results will be better If more data points are taken the results will also be better The results quoted here in can thus afford a guide in evaluating other situations If three compartments are being studied then the results would be the best that one could possibly achieve for the errors in four of the six parameters

SUMMARY

The effect of error in radiotracer data on the accuracy of derived parameters in two-compartment systems was studied Computer simulation was employed to produce data with error of different magnitude for each of several values of rate constant and amplitude The data were arranged to simulate experimental situations and analysed by non linear least squares For a given error in the data the calculated errors in the rate constants and amplitudes were defined in terms of their ratios and the number and spacing of the data points

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Der Einfluss der bei der Analyse mit radioaktiven Trägern entstandenen Datafehler auf die Genauigkeit der derivierten Parameter wurde studiert Bei Simulation mit einer Datenverarbeitungsmaschine wurden Datafehler verschiedener Grosse für jeden von mehreren

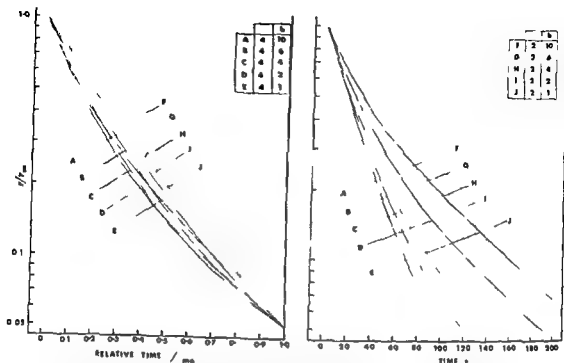


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Zahlwerten der Geschwindigkeitskonstanten und Amplituden produziert. Die Daten sollten experimentelle Bedingungen simulieren und wurden mit der Methode nicht linearer Mindest Quadrate analysiert. Für einen bestimmten Datafehler wurden die berechneten Fehler in Geschwindigkeitskonstanten und Amplituden als Funktionen der Verhältniszahlen der Konstanten und Amplituden sowie der Anzahl und Abstände der Datapunkte ausgedruckt.

RÉSUMÉ

L'auteur a étudié l'effet d'erreurs de mesures de radioactivité de traceurs sur l'exactitude des paramètres calculés à partir de ces mesures. Il a utilisé la simulation sur ordinateur pour obtenir des mesures entachées d'erreurs de différentes grandeurs pour chaque des différentes valeurs des constantes de vitesse et des amplitudes. Il a combiné ces mesures de façon à simuler des situations expérimentales et les a analysées par la méthode non linéaire des moindres carrés. Pour une erreur donnée de la mesure, il a calculé les erreurs sur les constantes de vitesse et sur les amplitudes pour différentes valeurs de leurs rapports et pour différents nombres et différents espacements des points de mesures.

REFERENCES

- BERMAN M. and SCHOENFELD R. Invariants in experimental data on linear kinetics and the formulation of models. *J. appl. Phys.* 27 (1956) 1361.
- SHAIN E. and WEISS M. F. The routine fitting of kinetic data to models. *Biophys. J.* 2 (1962) 275.
- BROWNELL G. L. and CALLAHAN A. B. Transform methods for tracer data analysis. *Ann. New York Acad. Sci.* 108 (1963) 172.
- KENDALL M. G. and STUART A. The advanced theory of statistics. 2 (1963) p. 83.
- MYHILL J. Analysis of radioisotope tracer data. *Proc. Symposium on Use of Computers in Medicine and Biology*. Melbourne 1965.
- Computer analysis of radioisotope tracer kinetic studies. *Proc. 6th Ann. Meeting on Physics in Medicine & Biology*. Melbourne 1966.
- (a) Effects of data error in two compartment analysis. *Proc. 7th Ann. Meeting on Physics in Medicine and Biology*. Adelaide 1967.
- (b) Effects of error on compartmental analysis. *Abstracts 7th Intern. Conf. Med. Biol. Eng.*, Stockholm 1967.
- (c) Investigation of the effect of data error in the analysis of biological tracer data. *Biophys. J.* 7 (1967) 903.
- Investigation of the effect of data error in the analysis of biological tracer data from three compartment systems. *J. theoret. Biol.* (in press 1968).
- WADSWORTH G. P. and BROWNELL G. L. Investigation of an operator method in the analysis of biological tracer data. *Biophys. J.* 5 (1965) 89.
- PIKE M. C. Random normal deviate. *Comm. A.C.M.* 8 (1965) 606.
- SHEPPARD C. W. and HOUSEHOLDER A. S. The mathematical basis of the interpretation of tracer experiments in closed steady state systems. *J. appl. Phys.* 22 (1951) 510.

INCIDENCE OF SECOND CANCERS AFTER RADON SEED THERAPY FOR CERVIX CANCER

by

JOHN GRAHAM and PAUL BURSTEIN

Addendum by S S KUROHARA

Radiotherapy is the standard treatment for invasive cancer of the uterine cervix. Nowadays intracavitary radium plus external roentgen is usually employed. A generation ago interstitial radon seeds were widely used instead of or in conjunction with intracavitary radiation. Because of some late complications and second cancers in radon seed treated cases we reviewed all cases of primary cervical cancer treated in our hospital from 1927—1953. We found that the frequency of other cancer formation and of radiation complications was influenced by the use of seeds.

In Table 1 are indicated the number of cases treated in five periods from 1927 to 1953. The method of treatment, the number surviving and the number of second cancers is shown in 5 year increments. A minimum follow up of 10 years is available for all. The usual treatment was a course of external roentgen therapy directed toward the mid pelvis given through 4 or 6 portals anterior, posterior and lateral. The central pelvic dose was given with about 1 000 R per week. It usually totalled 3 000 to 5 000 R and after an interval of about two weeks 10 to 12 gold radon seeds 1 mCi/seed were introduced in the cervix.

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Zahlwerten der Geschwindigkeitskonstanten und Amplituden produziert. Die Daten sollten experimentelle Bedingungen simulieren und wurden mit der Methode nicht linearer Mindest Quadraten analysiert. Für einen bestimmten Datafehler wurden die berechneten Fehler in Geschwindigkeitskonstanten und Amplituden als Funktionen der Verhältniszahlen der Konstanten und Amplituden sowie der Anzahl und Abstände der Datapunkte ausgedruckt.

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REFERENCES

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Table 1

Time of treatment survival rates and second cancers

Treatment period	Number of cases				0-5 years		5 year survival		6-10 years	
	Treated		2nd	Ca	2nd	Ca	c	s	c	s
	c	s	c	s						
	x		x		xx	xx			xx	xx
1927—	320	71	12	1	0	0	72	12	11	0
1931			4 %	1 %			22 %	17 %		
1932—	786	56	19	5	1	1	253	27	5	2
1936			2 %	9 %			32 %	48		
1937—	802	171	17	12	3	2	277	53	3	1
1941			2 %	7 %			34 %	31 %		
1912—	89	834	5	59	1	11	29	364	1	16
1946			6 %	7 %			33 %	44 %		
1947—	72	1 014	1	56	0	13	32	440	1	14
1953			1 %	6 %			44 %	43 %		
All	2 069	2 146	54	133	5	27	663	806	12	33
			2 7 %	6 2 %	0 8 %	3 %	32 %	42 %	2 3	4 6 %

c with radon seeds s without radon seeds x percentage of 2nd cancers calculated on base of treated cases listed in previous column xx percentage of 2nd cancers calculated on basis of treated cases listed in following column

An alternate method of completing the treatment was to apply intracavitary radium to bring the total dose at point A to 7 500 to 8 500 R. Favorable stage I cases were treated by intracavitary radium alone. Some patients who had a very good response to the roentgen with healing of the upper vagina and cervix had no seeds or radium. Patients with a large, bulky lesion after roentgen therapy were more likely to be given intracavitary radium than seeds. Others with progressive disease after the roentgen were given no further treatment. The overall character of the material in the two groups is rather similar in terms of age at time of treatment and clinical stage (see Table 2). The selection of patients for a particular form of treatment varied from time to time as can be seen from Table 1.

Two experienced gynecologists each reviewed all of the hospital records in a uniform manner. The data are summarized in Tables 1, 3 and 4. The follow up

Table 1 (cont.)

10-year survival		11-15 years		15-year survival		16-20 years		20 year survival		21+ years	
		2nd	Ca			2nd	Ca			2nd	Ca
c	s	c	s	c	s	c	s	c	s	c	s
		xx	xx			xx	xx			x	x
51	8	2	0	43	5	1	0	37	4	7	1
183	19	2	1	149	16	6	1	96	13	5	0
227	43	2	4	178	37	4	2	147	29	5	3
						11	3	275	46	17	4
						4*	6.5			6*	9/
297		1	18	13	231	2	11			0	3
		all 7	23	283	289						
		18	8								
31	347	0	22			0	7				
51	711	7	45	383	289	13	21	275	46	17	7

was complete in 98 % of all cases. The total number of cases treated with seeds and without seeds are approximately the same: $n = 2\ 069$ and $2\ 146$. The survival rate for the non seed cases is better than for those treated with seeds: 42 % versus 32 %. The difference probably is related to selection and time of treatment. The number surviving in each group through 15 years is roughly the same. There are more seed cases living at 20 years because more cases were treated with seeds in the early years.

The major radiation complications occurred in non seed cases more than twice as frequently as in seed cases in the first 15 years. This is probably explained by larger doses of total radiation given in the non seed group. The complications in the 16th to 20th year were about the same in both groups and the complication after the 21st year was in a seed case.

Second primary cancers are listed in Table 4. Adenocarcinomas of the uterine

body were accepted as second cancer if the cervical lesion was squamous. These occurred with about the same frequency in both groups. There were six uterine sarcomas in the non seed group and two in the seed cases. There were more cancers in non seed cases of almost all sites. Exceptions were adenocarcinoma of the corpus, carcinoma of the vagina and leukemia. Leukemia occurred in five seed cases and in two non seed cases. In seed cases this is ten times the incidence in the general population. Of the five cases, three were lymphatic, one myelogenous and one unknown. It is remarkable that all 18 of the skin cancers occurred in the non seed group. Second cancers occur more frequently in non seed cases at all intervals after treatment.

The non seed cases received a larger dose of radiation from both roentgen and radium than the seed cases. All of the exposure occurred within a brief period of a few weeks while treatment was given. The seed cases tended to have a lower integral dose. Perhaps of more importance is the prolonged low intensity radiation that they received from the retained seeds which contain radium D, the residue of radon (GRAHAM, GRAHAM, SOTTO & BAILY 1960). Radium D has a half life of 18 years. It emits beta rays of 1.17 MeV that excite the gold to generate a continuous spectrum of roentgen radiation with peaks at 70 and 167 keV. Seed cases are found to retain seeds in the region of the cervix for 20 or more years and the retained seeds usually have some residual, measurable radioactivity. The total dose from radium D is in the range of 100 to 300 rad.

From the present data it is impossible to determine whether the second cancers are more or less frequent than normal in these two groups. BELOVOSCHIKIN reported from Sweden that they found an incidence of 4.6% (61 in 1330) second cancers in cancer of the cervix patients six years or more after treatment. Their follow up ranged from 10 to 40 years. Their cases were treated with intracavitary radium and none with seeds. Comparable figures in our series are 12% (106 of 896) in the non seed cases and 7.4% (49 of 663) in the seed cases.

Radon seeds provide effective irradiation for cervical cancer. The cure and complication rates are comparable to those using other forms of treatment. The higher frequency of leukemia in seed cases is not unexpected in view of the protracted low intensity exposure. The remarkable finding is that other cancers occurred less than half as frequently in the seed cases. This cannot be explained by selection, for stage of disease, age, etc. are roughly the same. It is likely that the radon seeds exerted this effect. The gold is probably inert. One explanation is that prolonged low intensity radiation of radium D has a beneficial effect. Perhaps it stimulates the defense mechanism to oppose the development of new cancer.

This concept is contrary to mortality rates in radiologists who are assumed to be exposed to radiation more than others (SFLTSE & SARTWELL 1964). They

Table 2
Distribution of cases by age and clinical stage

Age	No seeds	Seeds
—29	3	3
30—39	16	17
40—49	29	30
50—59	27	30
60—69	18	15
70 or more	7	5
Clinical stage		
I	21	13
II	33	34
III	29	36
IV	17	17

Table 3
Major radiation complications

	Time after treatment of cervical cancer											
	0-5		6-10		11-15		16-20		21+		All	
	years		years		years		years		years			
	c	s	c	s	c	s	c	s	c	s	c	s
Bladder fistula	4	9	1				3	1			6	5
Rectal fistula	3	9		4			4	1	1	1	5	18
Recto-vaginal stricture			1	1			2		1		1	5
Vesico-vaginal fistula												1
Urethra-vaginal fistula			1									1
Ileocecal fistula			1									1
Ilial perforation			1									1
Totals	7	16	2	5	—	9	11	2	1	—	17	37

have a higher death rate from leukemia (19 observed versus 11 expected) and other cancers (135 observed versus 87 expected) than ophthalmologists and otolaryngologists. The character of irradiation and timing of exposure is quite different in our series and in radiologists. The carcinogenic property of ionizing radiation is well known (LITTLE 1966). Its stimulant effect on defense mechanisms is less familiar. Locally applied radiation will increase antibody production (GRAHAM & LESKOWITZ 1956; GRAHAM, GRAHAM, NERI & WRIGHT 1956) and mast cell concentration in the exposed area (GRAHAM & GRAHAM 1966).

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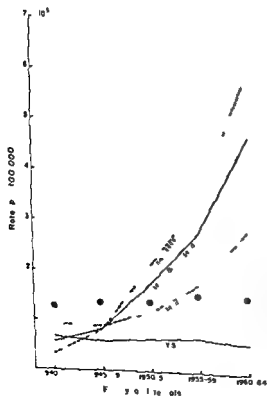
Addendum in proofs

by

S S KUROHARA

Second cancer incidence rates were calculated for cervical cancer patients treated with seeds alone or in combination with roentgen irradiation and for those treated with radium alone roentgen irradiation or both. These rates were based on the number of patients still alive (at risk to develop second cancers) during 5 year intervals beginning at 1940 and ending at 1964.

Since the age of occurrence of second primaries in these patients was 40 or more years, the New York State (exclusive of the city) rates for normal females for these age ranges were calculated from published data (FERBIE et coll 1962). The incidence rates of second cancer rise in both treatment groups from 1940 through 1964 are given in the figure below. These rates during 1940 to 1944 are very close to the normal one. The rise is significantly higher for the non-seed group than for the seed group.



Second cancer incidence rates plotted against 5 year chronologic time intervals. Cancer incidence rates for the normal female population over 40 years of age in New York State (exclusive of the city) are shown for these time intervals. The solid circles indicate New York State incidence rates corrected for age distribution of patients at risk. The rate of radon seed radiotherapy is significantly lower than that for non seed radiotherapy at time interval 1950-1964 ($P < 0.001$).

Table 4

Incidence and type of second cancers occurring after radon seed therapy for cervix cancer

	Time of occurrence after first treatment of cervix cancer											
	0—5		6—10		11—15		16—20		21+		All	
	years		years		years		years		years			
	\bar{c}	\bar{s}	\bar{c}	\bar{s}	\bar{c}	\bar{s}	\bar{c}	\bar{s}	\bar{c}	\bar{s}	\bar{c}	\bar{s}
Adenocarcinoma of uterine corpus	0	1	3	3	2	3	1	0	3	1	11	8
Uterine sarcoma & mixed	1	0	0	4	0	1	1	1	0	0	11	0
Carcinoma vulva	0	2	0	0	0	0	1	0	1	0	0	4
Carcinoma vagina	0	0	0	1	1	1	1	0	2	0	4	2
Carcinoma pelvis			0	1							0	1
Carcinoma ovary	0	1	0	4	1	5	1	0	0	1	7	11
Carcinoma breast	0	5	4	6	2	10	3	1	2	3	11	25
Carcinoma bladder	2	0	1	0	1	5	2	3	0	0	6	8
Carcinoma colon and rectum	0	6	2	3	0	5	3	5	4	0	9	19
Leukemia	1	0	2	1	0	1	0	0	2	0	5	2
Myeloma			0	1							0	1
Lymphoma					0	1	0	1			0	2
Carcinoma kidney			0	1					1	0	1	1
Carcinoma lung	1	1	0	4	0	6	1	1	0	1	2	13
Carcinoma liver									1	0	1	0
Carcinoma larynx									1	0	1	0
Carcinoma esophagus									1	0	1	0
Carcinoma stomach			0	1	0	1	0	2			0	4
Sarcoma stomach					0	1					0	1
Carcinoma pancreas							0	1			0	1
Carcinoma tongue	0	1									0	1
Carcinoma mouth					0	1					0	1
Lymphosarcoma tonsil					0	1					0	1
Carcinoma thyroid									0	1	0	1
Carcinoma brain					0	1					0	1
Carcinoma skin	0	10	0	2	0	1	0	5			0	18
Melanoma			0	1							0	1
All	5	27	12	33	7	45	13	21	17	7	54	133

Animal studies show that low intensity total body irradiation may increase longevity (CARLSON, SCHIEYER & JACKSON 1957, LORENZ, HOLICROFT, MILLER et coll 1955). However, there is an associated increase in tumor formation. We know of no animal studies where low intensity local radiation was given

- — SOTTO L B J and BAILEY V A Spent radon seeds I Late effects Radiology 74 (1960) 399
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- LITTLE J B Environmental hazards Ionizing radiation New Engl J Med 275 (1966) 929
- LORENZ F HOLLGROFT J W MILLER E et coll Long term effects of acute and chronic irradiation in mice I Survival and tumor incidence following chronic irradiation of 0.11 r per day J nat Cancer Inst 15 (1955) 1049
- SELTZER R and SARTWELL H The effect of occupational exposure to radiation on the mortality of physicians J Amer med Ass 190 (1964) 1046

SUMMARY

Study of patients with carcinoma of the cervix first seen in the period 1927—1953. Radiotherapy including radon seeds was given to 2 069 patients and without seeds to 2 146 patients. All were followed up for periods between 10 and 35 years. Age, stage, distribution and survival rates in the two groups were about the same. The frequency of secondary cancer in the non seed cases was twice that in the radon seed group. The difference is probably significant for it was found throughout the period of observation. The reason for the difference is not clear.

ZUSAMMENFASSUNG

Es wird über eine Studie an Patienten mit Cervixkarzinom berichtet, die erstens während der Periode 1927—1953 zur Untersuchung kamen. Radiotherapie einschliesslich Radon Samen wurde in 2 069 Patienten gegeben und Radiotherapie ohne Samen in 2 146 Patienten. Alle wurden über Perioden zwischen 10 und 35 Jahren beobachtet. Altersverteilung, Tumorstadium und Überlebensrate waren dieselben für die beiden Gruppen. Die Frequenz von Sekundärkrebs war doppelt so gross in der Gruppe, die keine Radonsamen erhielt, im Vergleich zur Radongruppe. Diese Differenz wurde während der ganzen Periode beobachtet und muss wahrscheinlich als signifikant betrachtet werden, obwohl die Ursache dieser Differenz nicht klar ist.

RÉSUMÉ

Les auteurs ont étudié le cancer du col de l'utérus chez des malades vues pour la première fois au cours de la période allant de 1927 à 1953. Le traitement de ces malades était radiothérapie comprenant l'implantation de grains de radon dans 2 069 cas et radiothérapie sans grains dans 2 146 cas. Les malades ont été suivies pendant 10 à 35 ans. L'âge, le stade, la distribution et le taux de survie étaient à peu près les mêmes dans les deux groupes. La fréquence d'un cancer secondaire chez les malades qui n'avaient pas eu de grains de radon a été double de celle du groupe traité par les grains de radon. Cette différence est probablement significative car on la retrouve pour toute la période d'observation. La raison de cette différence n'est pas claire.

REFERENCES

- BEJONOSCHIKIN II. Das Auftreten des Karzinoms nach der 5-jährigen Heilungsdauer des bestrahlten carcinoma colli uteri. *Acta radiol.* 44 (1955) 57.
- CARLSON L. D., SCHIEVER W. J. and JACKSON B. H. The combined effects of ionizing radiation and low temperature on the metabolism, longevity and soft tissue of the white rat. *Radiat. Res.* 7 (1957), 190.
- GRAHAM J. B. and LESKOWITZ S. Enhanced production of antibodies by local irradiation. II. Measurement of local antibodies. *J. Immunol.* 76 (1956) 110.
- GRAHAM R. M., NERI L. and WRICHT K. A. Enhanced production of antibodies by local irradiation. I. Measurement of circulating antibodies. *J. Immunol.* 76 (1956) 103.

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FROM THE RESEARCH LABORATORY OF MEDICAL ELECTRONICS (DIRECTOR PROF HENRY WALLMAN), CHALMERS UNIVERSITY OF TECHNOLOGY, AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR PROF MAGNUS STRANDQVIST) UNIVERSITY OF GOTHENBURG, SWEDEN

FIELD CONTROL IN ROENTGEN THERAPY WITH A 5 MeV LINEAR ACCELERATOR BY MEANS OF TELEVISION

by

ROLAND MALVEN, BINGT ROSENGREN and HENRY WALLMAN

Field control of direct roentgen irradiation from a 30 MeV betatron and direct gamma irradiation from a cobalt 60 unit were described in two previous publications (BENNER, ROSENGREN, WALLMAN & NERTELAND 1962 and MALVEN, ROSENGREN & WALLMAN 1965). The advantages of continuous and direct monitoring, especially in connection with the use of small fields, were pointed out in these articles. The technical difficulties involved in obtaining adequate contrast and detail were also discussed.

One of the therapeutically important advantages of high voltage radiation is the small difference in absorption between various tissues, this, however, necessarily implies low contrast. The possibility of contrast enhancement afforded by television techniques, combined with the use of either gold as an indicator, or air as negative contrast, makes it possible to achieve satisfactory reproduction.

Submitted for publication 8 August 1967

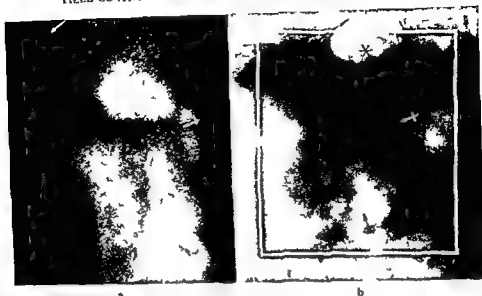


FIG. 1. Corresponding pair of accelerator television image (a) and roentgenogram obtained with 125 kV (b) from a patient with bladder insufflated with CO₂ (contrast level at *). Symphysis pubis (—) hip joint (—) Image (a) corresponds to area outlined in (b)

In the most recent paper (MALVEN *et coll* 1963) this contrast enhancement was exemplified by photographs taken from a television monitor screen during treatment of a gynecologic carcinoma with metastases in the pelvic wall marked by gold indicators. Other examples included insufflation of air into the bladder for a brief localization preceding the treatment itself (which should be given with an empty bladder), and use of the air present in the upper respiratory tract for observation of the laryngeal or pharyngeal tumours during treatment.

The technique was described in detail in the first paper (BENNER *et coll*). Mention was made in the second paper (MALVEN *et coll*) of the modifications arising from the use of a cobalt unit.

In the present contribution the use of this technique in connection with therapy with a 5 MeV linear accelerator will be described.

The radiation qualities with a gamma unit and a 5 MeV linear accelerator are therapeutically equivalent with a somewhat larger depth dose with the latter. The penumbra is, however considerably smaller in the case of the linear accelerator, in view of the fact that the focus is about 4 mm in diameter whereas the radiation source in our cobalt unit is 20 mm \times 20 mm

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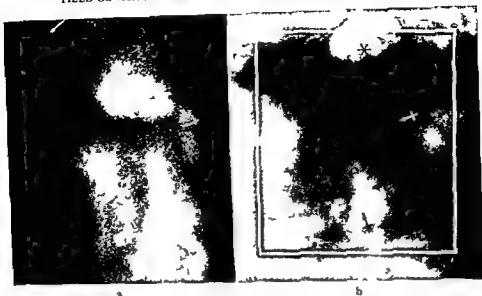


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Fig 3 Corresponding accelerator television image (a) and roentgenogram (b) from a patient with laryngeal carcinoma. Epiglottis (—→) inlet of larynx (v) vocal cord level (↔) trachea (*)

approximately the same extent in the two images. Definition is however less good in the accelerator television image although the anatomical details are sufficient to permit an orientation. It is also apparent from the television image that the medulla is not being irradiated.

A similar comparison was made in a case of laryngeal carcinoma as demonstrated in Fig 3.

Conclusion

The amount of detail in the high voltage roentgen television image cannot of course be compared with that in conventional roentgen films owing to the lower contrast produced by the high energy radiation. Another reason is that roentgenograms are usually obtained in projections selected in the manner most favourable from the diagnostic point of view. On the other hand the megavolt roentgen television images are based upon projections determined by the location of the field of treatment, these in turn being determined by considerations of optimal dose distribution. The megavolt



Fig 2 Corresponding pair of accelerator television image (a) and roentgenogram obtained with 125 kV (b) from a patient with tonsil tumour Filled teeth (—) soft palate (—) mandible (*)

in size. Better definition but somewhat poorer contrast should therefore be obtained in television monitoring with a linear accelerator in place of a cobalt unit.

The same technical equipment for field control in connection with these two therapeutic units was employed. Definition was better with the linear accelerator, although the improvement was not so great as could have been expected from a comparison of the focus sizes. The contrast was, as expected, somewhat poorer with the linear accelerator than with the cobalt unit.

A bladder in which gas (carbon dioxide) was insufflated previous to treatment is well outlined in Fig 1a, an indicator roentgenogram (125 kV) of the same patient in the same projection, is reproduced in Fig 1b. The negative contrast in the gas filled part of the bladder and in the rectum is satisfactory in the high voltage roentgen television image. The definition and the contrast are of course considerably poorer than in the roentgen film.

A corresponding pair of images from a patient with tonsil tumour treated with the linear accelerator are represented in Fig 2. The air is visible to



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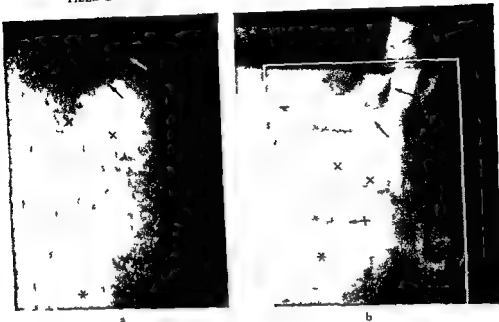


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images can, however, provide the radiation therapist with good localization of the field of treatment, and increasing experience in the interpretation of the appearances arising from the projections occurring in therapy will add considerably to their value

SUMMARY

A special system for field control in linear accelerator therapy is described and exemplified with treatments of the head-neck, and pelvic regions

ZUSAMMENFASSUNG

Ein neues Feldkontrollsystem für die Bestrahlung mit linearen Schleudern wird beschrieben und mit Beispielen für die Behandlung von Kopf-Hals und Becken illustriert

RÉSUMÉ

Les auteurs décrivent un système spécial de localisateur de champ pour le traitement par accélérateur linéaire et donnent des exemples de traitements des régions de la tête du cou et du bassin

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RÖNTGENTECHNISCHE ALLGEMEINE THEORIE

VON

L. CSÉPIN SZAY

Mehr als ein halbes Jahrhundert ist vergangen seitdem die Röntgentechnik in der ärztlichen Praxis erfolgreich angewendet wird. Trotzdem ist auf diesem Gebiete der Technik noch keine zusammenfassende allgemeine Theorie bekanntgemacht worden, die sämtliche bisherigen Ergebnisse zusammenfassen, auf das erzielbare Ideal hinweisen und eine Vergleichsbasis für die verschiedenen technischen Lösungen schaffen würde. Der Verfasser hat seine Theorie — vorwiegend in ihren regelungstechnischen Beziehungen — bereits früher veröffentlicht (1964), jedoch ausschliesslich für technische Fachleute und nicht vor einem internationalen Forum. Diesen Mangeln möchte ich jetzt durch Veröffentlichung meiner Arbeit ausführlicher als früher und vor dem internationalen Forum der röntgentechnisch interessierten Forscher abhelfen.

In den Jahren, die auf den zweiten Weltkrieg folgten, haben zahlreiche Forscher zum Ziele gesetzt, die praktischen und theoretischen Fragen in Verbindung mit der Weiterentwicklung der Röntgentechnik zu klären. So wird zum Beispiel — um nur einige von den vielen Forschern zu erwähnen — eine neue empirische Formel, die den Zusammenhang zwischen der Auf-

Bei der Redaktion am 24. Oktober 1967 eingegangen

images can, however, provide the radiation therapist with good localization of the field of treatment, and increasing experience in the interpretation of the appearances arising from the projections occurring in therapy will add considerably to their value

SUMMARY

A special system for field control in linear accelerator therapy is described and exemplified with treatments of the head, neck, and pelvic regions

ZUSAMMENFASSUNG

Ein neues Feldkontrollsystem für die Bestrahlung mit linearen Schleudern wird beschrieben und mit Beispielen für die Behandlung von Kopf, Hals und Becken illustriert

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Die Arbeiten der beispielsweise aufgezählten und auch der übrigen, hier infolge Platzmangel nicht erwähnten röntgenistischen Forscher werden dadurch charakterisiert, dass sie nicht bestrebt sind, die Ganze der Röntgentechnik betreffende, allgemein gültige Feststellungen zu machen, sondern sie befassen sich bezüglich der Vervollkommenung der Röntgentechnik nur mit einzelnen Teilproblemen und ihre Abhandlungen stützen sich auf statistische und empirische Angaben.

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Die Röntgentechnik wird in der Medizin hauptsächlich mit dem Ziel angewendet, um Informationen zu erhalten. Die Informationen erhalten wir von stehenden, oder bewegten Bildern durch visuelle Betrachtung. Träger des Informationsgehaltes sind die Helligkeitsunterschiede der einzelnen Bildpunkte (der einzelnen Flächenelemente). Die Beurteilung des Bildes, welche die Informationen vermittelt, ist immer subjektiv. Die Charakterisierung des 'guten Röntgenbildes' kann nicht durch einen einzigen Veränderlichen erfolgen, die Bildgüte können wir nur aus verschiedenen, subjektiv festgelegten Gesichtspunkten interpretieren. Nur aus diesem Standpunkt können wir einen funktionellen Zusammenhang aufstellen zwischen einer die Bildgüte charakterisierende Grösse und den veränderlichen Parametern der Röntgentechnik.

$$E = f_1(x_1, x_2, \dots, x_n) \quad (1)$$

wo E die Bildgüte charakterisierende Grösse, und x_1, x_2, \dots, x_n die Veränderlichen der Röntgentechnik sind. Nun besteht das Problem darin, dass wir diejenigen ausgezeichneten Werte $x_{1,0}, x_{2,0}, \dots, x_{n,0}$ der Veränderlichen x_1, x_2, \dots, x_n suchen, bei denen das subjektiv gewählte E auf einer

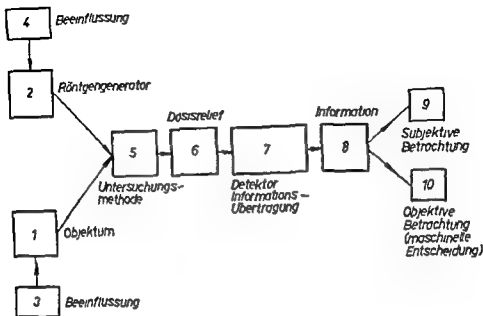


Abb 1 Schema der Informationsgewinnung in der Röntgentechnik

ebenfalls subjektiv festgelegten Skala irgendeinen für uns günstigen Wert, z. B. in gewisser Hinsicht das Optimum aufnimmt.

Wir sind der Meinung, dass für eine Theorie der Bildgestaltung, welche für die gesamte diagnostische Röntgentechnik gültig wäre, diese Betrachtungsweise nicht geeignet ist. An Stelle der absoluten Größen und Zusammenhänge soll man die Zusammenhänge der relativen Änderungen von sämtlichen Größen suchen, die in der Röntgentechnik vorkommen und massgebend für die Bildgestaltung sind. Das heisst, man soll die in der Röntgentechnik objektiv bestehenden Zusammenhänge beschreiben und dabei sämtliche subjektive Urteile ausschalten. Wir werden die Parameter der Röntgentechnik als relativ veränderte Größen darstellen, in zwei Gruppen anordnen und diejenige Gleichung

$$f_1\left(\frac{1x}{x_1}, \frac{\Delta x_2}{x_2}, \frac{\Delta x_k}{x_k}\right) = f_2\left(\frac{\Delta x_{k-1}}{x_{k-1}}, \frac{\Delta x_n}{x_n}\right) \quad (2)$$

suchen, die ein Gleichgewicht der relativen Änderungen darstellt, wobei $\frac{1x}{x_1}, \frac{1x}{x_2}, \frac{1x_k}{x_k}, \frac{\Delta x}{x_n}$ die relativen Änderungen der x_1, x_2, x_n

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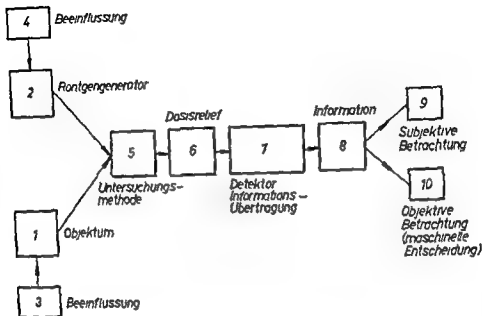


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Grossen bedeuten. Dadurch wird die Bestrebung auf die Bestimmung der Struktur, auf die Erforschung der objektiven inneren Zusammenhänge gerichtet.

Unter den bereits früher erwähnten Parametern der Röntgentechnik versteht man die Kennwerte der Aufbaukomponente des Informationsgewinnungsprozesses, wie z. B. die Röntgenrohrensprannung, der Rohrenstrom, die Belichtungszeit, usw. Die Aufbaukomponente der Informationsgewinnung sind aber die folgenden: die Röntgenstrahlen, das Objekt, usw. (Abb. 1). Unsere Bestrebung ist jetzt, den Zusammenhang, die Gesetzmässigkeiten zwischen diesen Kennwerten und das System der Beziehungen der Kennwerte innerhalb des gegebenen Prozesses zu bestimmen. Die Einheit der Kennwerte des Prozesses, ihr einheitliches System und ihr objektiver innerer Zusammenhang in den folgenden als die Struktur des Informationsgewinnungsprozesses bezeichnet.

Mit anderen Worten: wir können sämtliche Faktoren, die in der Röntgentechnik figurieren, in Betracht ziehen und ihre Wirkungen aufeinander und auf die Ganze in objektiver Weise bewerten. Mit Leichtigkeit können wir die Gültigkeitsgrenzen der Struktur — diejenigen Grenzen, bei welchen die quantitativen Änderungen noch nicht als qualitative Änderungen erscheinen — festlegen, sogar noch weiter gehend, wir können die Gültigkeit des Zusammenhangs (2), entsprechende approximative Zusammenhänge in Betracht ziehend, auf bestimmte Fälle der qualitativen Änderungen ausbreiten.

2 Mechanismus der Bildgestaltung (das Modell des Informationsgewinnungsprozesses) in der Röntgentechnik

Laut des Schemas der Röntgendiagnostik (siehe Abb. 1) gelangen die mit technischen Mitteln beeinflussten Röntgenstrahlen von gewünschter Qualität und Quantität (2 und 4 auf Abb. 1) mit dem entsprechend vorbereiteten Objekt, mit dem lebenden Organismus (1 und 3 auf Abb. 1) auf der durch die Untersuchungsmethode festgelegten Weise in Wechselwirkung (5), wodurch das Dosisrelief (6) entsteht.

Das Objekt ist meistens nicht homogen und die Strahlenintensität wird in den verschiedenen Flächenelementen der Bildebene — diese Ebene, wo die für die Bildgestaltung ausgenutzte Strahlenenergie aufgefangen wird, nennen wir folgend einfach die Bildebene — hinter dem Objekt unterschiedlich. Es besteht also die Möglichkeit, die verschiedenen Intensitätswerte durch ein Relief darzustellen, daher stammt der allgemein gebrauchte Ausdruck 'Strahlenrelief'. Auf Grund von ähnlichen Überlegungen kann hinter dem Objekt die zu jedem Flächenelement der Bildebene gehörende Dosis

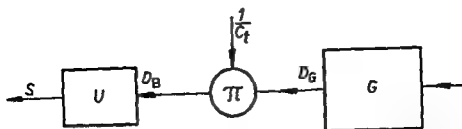


Abb 2 Vereinfachtes Schema (das Modell) der Informationsgewinnung in der Röntgentechnik

(exposure) durch ein Dosisrelief die unterschiedliche Helligkeit des Leuchtschirmes durch Helligkeitsrelief und die unterschiedliche Schwarzung des Filmes durch Schwarzungsrelief dargestellt werden

Nach der Detektierung und Informationsübertragung (7 auf Abb 1) kommt die Reihe an die subjektive (9) oder objektive (10, maschinelle Entscheidung) Betrachtung der Information (8)

Auf dem vereinfachten Schema — auf dem Modell — des jetzt erörterten Prozesses zur Informationsgewinnung (Abb 2) bedeutet D_B die Dosis welche hinter dem Objekt in einem Flächenelement der Bildebene der dort herrschenden Strahlenenergie entspricht und D_G denjenige Dosis, welche vom Rohrenbrennfleck in Einheitsabstand gemessen durch den Röntgengenerator (G) erzeugt wird und gleichzeitig für den Generator charakteristisch ist

Der im folgenden benutzte Ausdruck 'Dosis' und 'Dosisleistung' entspricht der physikalischen Konzeption vom exposure und 'exposure rate' nach ICRU. Wollten wir eine völlige Exaktheit bestreben müsste man die Begriffe, 'Strahlenenergie und Strahlenintensität' benutzen. Weil aber die Dosismessung in der Praxis ein verbreitetes Messverfahren ist, und weil in unserem Falle die Dosis (exposure) und die Dosisleistung (exposure rate) mit der Strahlenenergie und mit der Strahlenintensität proportional betrachtet werden kann, ferner weil die theoretische Überlegungen dadurch nicht beeinflusst werden in den folgenden Betrachtungen benutzen wir weiterhin die Begriffe Dosis und Dosisleistung.

C_t ist der Faktor der Wechselwirkung zwischen Objekt und Strahlung. Zum Schluss stellt S (beispielsweise in der Aufnahmetechnik) die Filmschwarzung dar. S bedeutet im allgemeinen die Helligkeit eines Flächenelementes im Bild welches die Information übermittelt.

Die im Vorangehenden vorkommende Größen D_B und D_G können eine Dosis (exposure) bedeuten aber auch eine Dosisleistung (exposure rate) z. B. bei Durchleuchtung oder Röntgenkinesmatographie. Der Buchstabe τ bedeutet eine Multiplikation.

Grossen bedeuten. Dadurch wird die Bestrebung auf die Bestimmung der Struktur, auf die Erforschung der objektiven inneren Zusammenhänge gerichtet.

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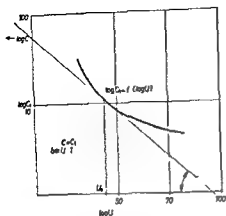


Abb 3 Änderung des Logarithmus des Objektparameters in der Funktion des Logarithmus der Röntgenohrspannung

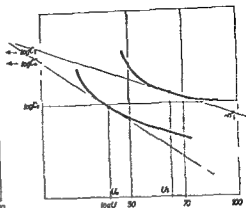


Abb 4 Funktion von $\log C_t = f(\log U)$ in zwei verschiedenen Aufnahmesituationen

mittelwert welcher zum Dosisrelief des ganzen Bildes gehört (womöglich klein gehalten wird) (Im entgegengesetzten Falle gehört zum Dosismittelwert infolge der Nichtlinearität, nicht der Schwarzungswert gemäss der Gradationskurve sondern ein kleinerer Wert) Falls die Bildzone auf diese Weise ausgewählt wird können wir im Kenntnis der Bildzone den richtigen Schluss mit Bezug auf das ganze Bild ziehen. Die richtig gewählten Zonen können als Stellen der Musterziehung betrachtet werden (siehe STIEVE 1957 WIDENMANN u. Mitarb 1962)

Nach dem vorher gesagten werden in dem folgenden die relative Änderung der Dosis (exposure) des Objektparameters und der Helligkeit (Schwarzung) und der Zusammenhang dieser relativen Änderungen unter einander bestimmt

3 Die relative Änderung der Dosis (exposure)

Im Sinne des Zusammenhanges (3) ist C_t einer festgelegten röntgentechnischen Situation ausschliesslich von dem Scheitelwert der Spannung U und von ihrem zeitlichen Ablauf abhängig (In dem folgenden wird U_s einfach mit U und I_m einfach mit I bezeichnet) Also

$$C_t = f_1(U) \quad (5)$$

da (5) kontinuierlich ist und eine begrenzte Funktion aus ihr gebildet werden kann

$$\log C_t = f_2(\log U) \quad (6)$$

Im allgemeinen ist also bezüglich eines Flächenelementes der Bildebene folgender Zusammenhang gültig

$$D_R \cdot G_t = D_c \quad (3)$$

wo G_t eine gut bestimmbare Zahl ohne Dimension ist, die von den Umständen der Aufnahme und von den Eigenschaften der Strahlen — auch vom Scheitelwert der Rohrensprannung und von ihrem zeitlichen Ablauf — abhängig ist

Die Bedeutung des Zusammenhanges (3) besteht darin, dass mit seiner Hilfe der Einfluss des Röntgenapparates, D_c , der Untersuchungsbedingungen und des Objekt-Strahlung-Zusammenwirkens, G_t , der Bildgestaltung (des Detektierens D_R) und der Informationsübertragung, S , getrennt erwogen werden können

Die Dosis (exposure), erzeugt durch Benutzung der elektrischen Energie, lautet im Sinne des gut bekannten Zusammenhanges, welches für die späteren als Grundlage dient, wie folgt

$$D_0 = b \cdot I_m \cdot U_s \cdot \tau \cdot \eta \cdot \varrho \cdot \xi \quad (4)$$

wobei I_m der Mittelwert des Rohrenstromes ist, U_s der Scheitelwert der Rohrensprannung, τ ist die Aufnahmezeit, η ein Faktor, die Strahlenausbeute, ϱ der Wirkungsgrad, ϱ ein Faktor, welcher den zeitlichen Ablauf des Rohrenstromes charakterisiert und auch von der Grösse abhängig ist, ξ ein Faktor der den zeitlichen Ablauf der Rohrensprannung charakterisiert, und b ist eine Konstante. Wir bemerken, dass für den Mittelwert der Dosisleistung (exposure rate) eine ähnliche Formel erhalten wird, worin aber die Zeit τ nicht vorkommt

Kehren wir jetzt zum Zusammenhang (3) zurück. Im allgemeinen hat D_R in den verschiedenen Flächenelementen der Bildebene einen anderen Wert. Der Zusammenhang (3) kann aber im allgemeinen Falle bezüglich bestimmten entsprechend gewählten Zonen und im speziellen Falle — z. B. wenn das Pläntom homogen und überall von der gleichen Dicke ist — auf das ganze Bild verallgemeinert werden. In solchem Falle braucht der Zusammenhang (3) nicht punktweise in Betracht gezogen werden, er ist nur mit Bezug auf je eine Zone des Bildes zu bewerten. Die Dosis (exposure) entspricht also in diesen Fällen dem arithmetischen Dosismittelwert des partiellen Dosisreliefs, das zur Bildzone gehört. Da zum Beispiel bei Aufnahmen die Übertragung vom Dosisrelief auf das Schwarzungsrelief, infolge der Form der Gradationskurve, nicht-linear ist, soll die Bildzone gewählt werden, dass der Mittelwert der interzonalen Dosisabweichungen bezogen auf die Zonenfläche, verglichen mit dem arithmetischen Dosis

Die relative Dosisänderung ist

$$D_r = \frac{D_{B_1} - D_{B_0}}{D_{B_0}} \quad (13)$$

Durch Substitution von (11) und (12) wird aus (13)

$$\begin{aligned} D_r &= \left(\frac{D_{G_1}}{C_{I_1}} - \frac{D_{G_0}}{C_{I_0}} \right) \frac{C_{I_0}}{D_{G_0}} = \\ &= \left(\frac{D_{G_1} U_1}{C_1} - \frac{D_{G_0} U}{C_0} \right) \frac{C_0}{D_{G_0} U_0^{n_0}} \end{aligned} \quad (14)$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren denselben in (14)

$$D_{G_1} = b I_1 U_1^{n_1} \tau_1 \eta_1, \quad D_{G_0} = b I_0 U_0^{n_0} \tau_0 \eta_0$$

Also

$$\begin{aligned} D_r &= \frac{\frac{b I_1 U_1^{n_1} \tau_1 \eta_1 U_1}{C_1} - \frac{b I_0 U_0^{n_0} \tau_0 \eta_0 U}{C_0}}{\frac{b I_0 U_0^{n_0} \tau_0 \eta_0 U_0^{n_0}}{C_0}} = \\ &= \frac{\frac{b I_1 \tau_1 \eta_1 U_1^{n_1+2}}{C_1} - \frac{b I_0 \tau_0 \eta_0 U_0^{n_0+2}}{C_0}}{\frac{b I_0 \tau_0 \eta_0 U_0^{n_0+2}}{C_0}} \end{aligned}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I, \quad U_1 = U_0 + \Delta U, \quad \tau_1 = \tau_0 + \Delta \tau \text{ ist}$$

$$\text{und } I_r = \Delta I / I_0, \quad U_r = \Delta U / U_0, \quad \tau_r = \Delta \tau / \tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon_0, \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D_r = \frac{\frac{b I (1 + I_r) [U (1 + U_r)]^{\varepsilon_1} \tau_0 (1 + \tau_r) \eta_1}{C_1} - \frac{b I_0 U_0^{\varepsilon_0} \tau_0 \eta_0}{C_0}}{\frac{b I_0 U_0^{\varepsilon_0} \tau_0 \eta_0}{C_0}}$$

Funktion und auch ihr Differentialquotient

$$\frac{d \log C_t}{d \log U} = -n (\log U) \quad (7)$$

wo n die Richtungstangente der Berührungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von $\log U$ ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

$$\left(\frac{d \log C_t}{d \log U} \right)_{U_0} = -n_0 (\log U_0) \quad (8)$$

Die Gleichung des Geraden, konstruiert mit dem Richtungstangens (8), ist

$$\log C_t = -n_0 \log U + \log C \quad (9)$$

Die Einführung der logarithmischen Funktion (6) war deshalb notwendig, weil die Richtungstangente n , welche mit ihrer Hilfe bestimmt wurde, einen einfachen, zweckentsprechenden Ausdruck von C_t ermöglicht. Auf Grund von (9) wird nämlich die Spannung U_0 folgendermassen gestrichet

$$C_t = \frac{C}{U_0} \quad (10)$$

Nehmen wir jetzt als Grundlage, zwei röntgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Rohrenstrom, τ_0 Aufnahmezeit, η_0 Rohrenwirkungsgrad gemacht (Einfachheit halber werden jetzt die Faktoren ρ und ξ vernachlässigt und b konstant genommen, aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen). Der Objektparameter (Abb. 4) ist

$$C_{t0} = \frac{C_0}{U_0^n} \quad (11)$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Rohrenstrom, τ_1 Aufnahmezeit, η_1 Rohrenwirkungsgrad gemacht und der Parameter des Objektes ist

$$C_{t1} = \frac{C_1}{U_1^n} \quad (12)$$

Die relative Dosisänderung ist

$$D_r = \frac{D_{B_1} - D_{B_0}}{D_{B_0}} \quad (13)$$

Durch Substitution von (11) und (12) wird aus (13)

$$\begin{aligned} D_r &= \left(\frac{D_{G_1}}{C_{I_1}} - \frac{D_{G_0}}{C_{I_0}} \right) \frac{C_{I_0}}{D_{G_0}} = \\ &= \left(\frac{D_{G_1} U_1}{C_1} - \frac{D_{G_0} U_0}{C_0} \right) \frac{C_0}{D_{G_0} U_0} \end{aligned} \quad (14)$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren den selben in (14)

$$D_{G_1} = b I_1 U_1^{\tau_1 \eta_1} \quad D_{G_0} = b I_0 U_0^{\tau_0 \eta_0}$$

Also

$$\begin{aligned} D_r &= \frac{\frac{b I_1 U_1^{\tau_1 \eta_1} U_1}{C_1} - \frac{b I_0 U_0^{\tau_0 \eta_0} U_0}{C_0}}{\frac{b I_0 U_0^{\tau_0 \eta_0} U_0}{C_0}} = \\ &= \frac{\frac{b I_1 \tau_1 \eta_1 U_1}{C_1} + 2}{\frac{b I_0 \tau_0 \eta_0 U_0}{C_0} + 2} \end{aligned}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta \tau \text{ ist}$$

$$\text{und } I_r = \Delta I / I_0 \quad U_r = \Delta U / U_0 \quad \tau_r = \Delta \tau / \tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D = \frac{\frac{b I (1 + I_r) [U_0 (1 + U_r)]^{\tau_0 (1 + \tau_r) \eta_1}}{C_1} - \frac{b I_0 U_0^{\tau_0 \eta_0}}{C_0}}{\frac{b I_0 U_0^{\tau_0 \eta_0}}{C_0}}$$

Funktion und auch ihr Differentialquotient

$$\frac{d \log C_t}{d \log U} = -n (\log U) \quad (7)$$

wo n die Richtungstangente der Berührungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von $\log U$ ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

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Die Gleichung des Geraden, konstruiert mit dem Richtungstangens (8), ist

$$\log C_t = -n_0 \log U + \log C \quad (9)$$

Die Einführung der logarithmischen Funktion (6) war deshalb notwendig, weil die Richtungstangente n , welche mit ihrer Hilfe bestimmt wurde, einen einfachen, zweckentsprechenden Ausdruck von C_t ermöglicht. Auf Grund von (9) wird nämlich die Spannung U_0 folgendermassen gestrichet

$$C_t = \frac{C}{U_0} \quad (10)$$

Nehmen wir jetzt als Grundlage, zwei röntgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Rohrenstrom, τ_0 Aufnahmezeit, η_0 Rohrenwirkungsgrad gemacht (Einfachheit halber werden jetzt die Faktoren ρ und ξ vernachlässigt und l konstant genommen, aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen). Der Objektparameter (Abb. 1) ist

$$C_{t,0} = \frac{C_0}{U_0} \quad (11)$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Rohrenstrom, τ_1 Aufnahmezeit, η_1 Rohrenwirkungsgrad gemacht und der Parameter des Objektes ist

$$C_{t,1} = \frac{C_1}{U_1} \quad (12)$$

Die relative Dosisänderung ist

$$D_r = \frac{D_{B1} - D_{B0}}{D_{B0}} \quad (13)$$

Durch Substitution von (11) und (12) wird aus (13)

$$\begin{aligned} D_r &= \left(\frac{D_{G1}}{C_{t1}} - \frac{D_{G0}}{C_{t0}} \right) \frac{C_{t0}}{D_{G0}} = \\ &= \left(\frac{D_{G1} U_1}{C_1} - \frac{D_{G0} U}{C_0} \right) \frac{C_0}{D_{G0} U_0} \end{aligned} \quad (14)$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren den selben in (14)

$$D_{G1} = b I_1 U_1^{\tau_1 \eta_1} \quad D_{G0} = b I_0 U_0^{\tau_0 \eta_0}$$

Also

$$\begin{aligned} D_r &= \frac{\frac{b I_1 U_1^{\tau_1 \eta_1} U_1}{C_1} - \frac{b I_0 U_0^{\tau_0 \eta_0} U_0}{C_0}}{\frac{b I_0 U_0^{\tau_0 \eta_0} U_0}{C_0}} = \\ &= \frac{\frac{b I_1 \tau_1 \eta_1 U_1^{+2}}{C_1} - \frac{b I_0 \tau_0 \eta_0 U_0^{+2}}{C_0}}{\frac{b I_0 \tau_0 \eta_0 U_0^{+2}}{C_0}} \end{aligned}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta \tau \text{ ist}$$

$$\text{und } I = \Delta I / I_0 \quad U_r = \Delta U / U_0, \quad \tau_r = \Delta \tau / \tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon_0 \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D_r = \frac{\frac{b I (1 + I_r) [U (1 + U)]^{\tau_0 (1 + \tau_r) \eta_1}}{C_1} - \frac{b I_0 U_0^{\tau_0 \eta_0}}{C_0}}{\frac{b I_0 U_0^{\tau_0 \eta_0}}{C_0}}$$

Funktion und auch ihr Differentialquotient

$$\frac{d \log C_t}{d \log U} = -n (\log U) \quad (7)$$

wo n die Richtungstangente der Berührungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von $\log U$ ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

$$\left(\frac{d \log C_t}{d \log U} \right)_{U_0} = -n_0 (\log U_0) \quad (8)$$

Die Gleichung des Graden, konstruiert mit dem Richtungstangens (8), ist

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Die Einführung der logarithmischen Funktion (6) war deshalb notwendig, weil die Richtungstangente n , welche mit ihrer Hilfe bestimmt wurde, einen einfachen, zweckentsprechenden Ausdruck von C_t ermöglicht. Auf Grund von (9) wird nämlich die Spannung U_0 folgendermassen gestaltet

$$C_t = \frac{C}{U_0} \quad (10)$$

Nehmen wir jetzt als Grundlage, zwei röntgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Rohrenstrom, τ_0 Aufnahmezeit, η_0 Rohrenwirkungsgrad gemacht. (Einflussfaktoren werden jetzt die Faktoren ϱ und ξ vernachlässigt und b konstant genommen, aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen.) Der Objektparameter (Abb. 1) ist

$$C_{t,0} = \frac{C_0}{U_0^n} \quad (11)$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Rohrenstrom, τ_1 Aufnahmezeit, η_1 Rohrenwirkungsgrad gemacht und der Parameter des Objektes ist

$$C_{t,1} = \frac{C_1}{U_1^n} \quad (12)$$

Die relative Dosisänderung ist

$$D_r = \frac{D_{B1} - D_{B0}}{D_{B0}} \quad (13)$$

Durch Substitution von (11) und (12) wird aus (13)

$$\begin{aligned} D_r &= \left(\frac{D_{G1}}{C_{t1}} - \frac{D_{G0}}{C_{t0}} \right) \frac{C_{t0}}{D_{G0}} = \\ &= \left(\frac{D_{G1} U_1^2}{C_1} - \frac{D_{G0} U_0^2}{C_0} \right) \frac{C_0}{D_{G0} U_0^2} \end{aligned} \quad (14)$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren den selben in (14)

$$D_{G1} = b I_1 U_1^2 \tau_1 \eta_1 \quad D_{G0} = b I_0 U_0^2 \tau_0 \eta_0$$

Also

$$\begin{aligned} D_r &= \frac{\frac{b I_1 U_1^2 \tau_1 \eta_1 U_1^2}{C_1} - \frac{b I_0 U_0^2 \tau_0 \eta_0 U_0^2}{C_0'}}{\frac{b I_0 U_0^2 \tau_0 \eta_0 U_0^2}{C_0}} = \\ &= \frac{\frac{b I_1 \tau_1 \eta_1 U_1^2}{C_1} - \frac{b I_0 \tau_0 \eta_0 U_0^2}{C_0}}{\frac{b I_0 \tau_0 \eta_0 U_0^2}{C_0}} \end{aligned}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta \tau \text{ ist}$$

$$\text{und } I = \Delta I / I_0 \quad U_r = \Delta U / U_0, \quad \tau_r = \Delta \tau / \tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D = \frac{\frac{b I_0 (1+I_r) [U (1+U_r)]^2 \tau_0 (1+\tau_r) \eta_1}{C_1} - \frac{b I_0 U_0^2 \tau_0 \eta_0}{C_0}}{\frac{b I_0 U_0^2 \tau_0 \eta_0}{C_0}}$$

Jetzt nehmen wir an, dass $\varepsilon_1 = \varepsilon_0 + \Delta\varepsilon$, dann $n_1'' - n_0 = \Delta n = \Delta\varepsilon$ und

$$D_r = \frac{\frac{bI_0(1+I_r)U_0^{\varepsilon_0}(1+U_r)^{\varepsilon_0+1}U_0^{\varepsilon_0}\tau_0(1+\tau_r)\eta_1}{C_1} - \frac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0}}{\frac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0'}} \quad (15)$$

— Da $(1+I_r)(1+\tau_r)$ mit $(1+Q_r)$ gleich ist, wobei

Q_r die relative Änderung der mAs bedeutet, wird also (15) nach dividieren mit $bI_0U_0^{\varepsilon_0}\tau_0\eta_0/C_0$

$$D_r = \frac{\eta_1}{\eta_0} \frac{C_0'(1+Q_r)(1+U_r)^{2+\varepsilon_0+1}U_0^{\varepsilon_0}}{C_1'} - 1 \quad (16)$$

$$\text{oder } 1+D_r = \frac{\eta_1}{\eta_0} \frac{(1+Q_r)(1+U_r)^2}{\frac{(1+U_r)^{-n_1}U_0^{-1}C_1}{C_0'}} \quad (17)$$

4 Die relative Änderung des Objektparameters

In dem nachstfolgenden werden wir zeigen, dass der Nenner des zweiten Teils des Zusammenhanges (17) mit der relativen Änderung des Objektparameters $C_{t,r}$ in einfacher Weise ausgedrückt werden kann. Aus der Abb. 1 folgt

$$\log C_{t,1} = -n_1 \log U_1 + \log C_1 \quad (18)$$

$$\text{und } \log C_{t,0} = -n_0 \log U_0 + \log C_0 \quad (19)$$

Also

$$\begin{aligned} \log C_{t,1} - \log C_{t,0} &= \log(1+C_{t,r}) = \\ &= -n_1 \log U_1 + \log C_1 + n_0 \log U_0 - \log C_0 \end{aligned}$$

$$\text{woraus } (1+C_{t,r}) = \frac{(1+U_r)^{-n_1}U_1^{-1}C_1}{C_0} \quad (20)$$

Im Spezialfalle, z. B. bei einer Röntgenaufnahme, wird die Gradationskurve mit einer Gerade angenähert. Selbstverständlich kann die Übertragungskurve — in diesem Falle die Gradationskurve — auch anders approximiert werden. Dann erhalten wir bezüglich der relativen Änderung der Schwärzung (Abb. 5) den folgenden Zusammenhang

$$S_r = \frac{S_r - S_0}{S_0} = \frac{\gamma}{S_0} \log(1+D_r) \quad (21)$$

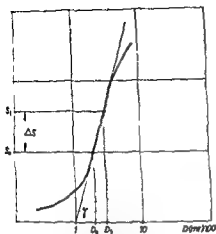


Abb 5 Film Schwarzungskurve und deren Annäherung mit einem Geraden

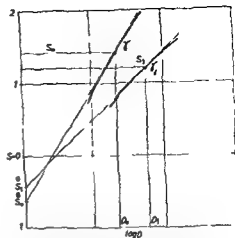


Abb 6 Annäherung der Gradationskurven zur Bestimmung der Grundgleichung der Röntgenaufnahme-technik

wo S_0 die zur Dosis (exposure) D_0 gehörende Schwarzung und γ die Richtungstangente der Gradationskurve bedeutet. Durch Substitution der Zusammenhänge (17) und (20) in (21) erhalten wir einen grundlegenden Zusammenhang der allgemeinen Theorie in der Röntgenaufnahme-technik bezüglich der relativen Schwarzungsänderung

$$S_r = \frac{\gamma}{S_0} \log \frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_{tr})} \quad (22)$$

Falls die Übertragungskurve bezüglich der relativen Änderungen mit Geraden approximiert wird und a (im Falle von $S_0 = 1$ und $\gamma = 1$) die Richtungstangente der Gerade bedeutet, so wird

$$S_r \approx \frac{\gamma}{S_0} a \left[\frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_{tr})} - 1 \right] \quad (23)$$

In den obigen Zusammenhängen wird im allgemeinen

$$C_{tr} = \frac{(1+U)^{-1} U^{-A} C_1}{C_0} - 1 \quad (24)$$

und falls $\Delta n \rightarrow 0$ $n_1 \approx n_0 \approx n$ dann wird

$$C_{tr} \approx \frac{(1+U_r)}{C_0} C_1 - 1 \quad (25)$$

Jetzt nehmen wir an, dass $\varepsilon_1 = \varepsilon_0 + \Delta\varepsilon$, dann $n_1' - n_0' = \Delta n = \Delta\varepsilon$ und

$$D_r = \frac{\frac{bI_0(1+I_r)U_0^{\varepsilon_0}(1+U_r)^{\varepsilon_0+\Delta\varepsilon}U_0^{\Delta\varepsilon}\tau_0(1+\tau_r)\eta_1}{C_1} - \frac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0}}{\frac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0}} \quad (15)$$

— Da $(1+I_r)(1+\tau_r)$ mit $(1+Q_r)$ gleich ist, wobei

Q_r die relative Änderung der mAs bedeutet, wird also (15) nach dividieren mit $bI_0U_0^{\varepsilon_0}\tau_0\eta_0/C_0$

$$D_r = \frac{\eta_1}{\eta_0} \frac{C_0(1+Q_r)(1+U_r)^{2+\varepsilon_0+\Delta\varepsilon}U_0^{\Delta\varepsilon}}{C_1} - 1 \quad (16)$$

$$\text{oder } 1 + D_r = \frac{\eta_1}{\eta_0} \frac{(1+Q_r)(1+U_r)^{\varepsilon_0+\Delta\varepsilon}}{\frac{(1+U_r)^{-\varepsilon_0}U_0^{-\Delta\varepsilon}C_1}{C_0}} \quad (17)$$

4 Die relative Änderung des Objektparameters

In dem nachstfolgenden werden wir zeigen, dass der Nenner des zweiten Teils des Zusammenhanges (17) mit der relativen Änderung des Objektparameters $C_{t,r}$ in einfacher Weise ausgedrückt werden kann. Aus der Abb. 4 folgt

$$\log C_{t,1} = -n_1 \log U_1 + \log C_1 \quad (18)$$

$$\text{und } \log C_{t,0} = -n_0 \log U_0 + \log C_0 \quad (19)$$

Also

$$\begin{aligned} \log C_{t,1} - \log C_{t,0} &= \log(1+C_{t,r}) = \\ &= -n_1 \log U_1 + \log C_1 + n_0 \log U_0 - \log C_0' \\ \text{woraus } (1+C_{t,r}) &= \frac{(1+U_r)^{-n_1} U_0^{-\Delta n} C_1}{C_0} \text{ ist} \end{aligned} \quad (20)$$

Im Spezialfalle, z. B. bei einer Röntgenaufnahme, wird die Gradationskurve mit einer Geraden angenähert. Selbstverständlich kann die Übertragungskurve — in diesem Falle die Gradationskurve — auch anders approximiert werden. Dann erhalten wir bezüglich der relativen Änderung der Schwarzung (Abb. 5) den folgenden Zusammenhang

$$S_r = \frac{S_1 - S_0}{S_0} = \frac{\gamma}{S_0} \log(1 + D_r) \quad (21)$$

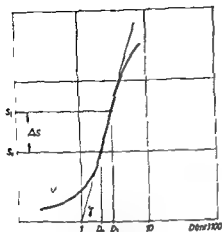


Abb 5 Filmcharakteristik und deren Annäherung mit einer Geraden

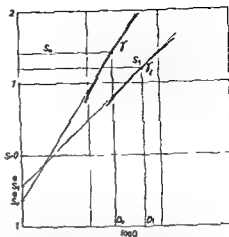


Abb 6 Annäherung der Gradationskurven zur Bestimmung der Grundgleichung der Röntgenaufnahme-technik

wo S_0 die zur Dosis (exposure) D_0 gehörende Schwarzung und γ die Richtungstangente der Gradationskurve bedeutet. Durch Substitution der Zusammenhänge (17) und (20) in (21) erhalten wir einen grundlegenden Zusammenhang der allgemeinen Theorie in der Röntgenaufnahme-technik bezüglich der relativen Schwarzungsänderung

$$S_r \approx \frac{\gamma}{S_0} \log \frac{\eta_1 (1+U_r) (1+Q_r)}{\eta_0 (1+C_{tr})} \quad (22)$$

Falls die Übertragungskurve bezüglich der relativen Änderungen mit Geraden approximiert wird und α (im Falle von $S_0 = 1$ und $\gamma = 1$) die Richtungstangente der Gerade bedeutet, so wird

$$S_r \approx \frac{\gamma}{S_0} \alpha \left[\frac{\eta_1 (1+U_r) (1+Q_r)}{\eta_0 (1+C_{tr})} - 1 \right] \quad (23)$$

In den obigen Zusammenhängen wird im allgemeinen

$$C_{tr} = \frac{(1+U)^{-1} U^{-1} C_1}{C_0} - 1 \quad (24)$$

und falls $\Delta n \rightarrow 0$ $n \approx n_0 \approx n$ dann wird

$$C_{tr} = \frac{(1+U)^{-1} C_1}{C_0} - 1 \quad (25)$$

und zum Schluss, wenn $C_0' \approx C_1$, so wird

$$C_{1r} = (1 + U_r)^{-n} - 1 \quad (26)$$

In praktischen Fällen ist es zweckmässig, den Ausdruck C_{1r} die Funktion der relativen Änderungen, welche das Objekt, oder das Prüfverfahren charakterisieren (z. B. Dicke, Abstand, Raster, usw.) zu bestimmen und in (22) substituieren (Eine nähere Auseinandersetzung werden wir ein andermal behandeln)

5. Relative Änderung von S allgemeine Gleichung (Struktur des Systems)

Die Zusammenhänge unserer bisherigen Ableitungen (22) und (23) sind nur in beschränktem Masse gültig, da sie die relativen Änderungen sämtlicher Parameter der Detektierung und der Übertragung der Information nicht in Betracht ziehen. Die spannungsabhängige Änderung der Filmempfindlichkeit wurde z. B. nicht in Betracht gezogen. Suchen wir die Struktur irgendeines Verfahrens der Röntgentechnik, so geht man folgendermassen vor: vorerst wird die relative Änderung der informationserteilenden S , als Funktion der relativen Änderung der Bilddosis (exposure)

$$S_r = f_1(D_{Br})$$

dann substituieren wir die bereits bekannte Funktion

$$D_{Br} = f_2(C_{1r}, D_{Or})$$

in diesem Zusammenhang. Die Struktur des Systems, d. h. die Gleichung des röntgentechnischen Verfahrens wird so gewonnen, wenn wir $S_r = 0$ machen

Das bisher Gesagte demonstrieren wir in Bezug auf die Röntgenaufnahme-technik. Zur Bestimmung der relativen Änderung der Schwarzung haben wir zwei verschiedene Schwarzungskurven aufgenommen (Abb. 6). In dem ersten Falle soll zur Dosis D_0 die Schwarzung S_0 und die Gamma der Gridationskurve γ_0 sein. In diesem Falle wird

$$S_0 = \gamma_0 \log D_0 + S_0^* \quad (27)$$

In anderem Falle

$$S_1 = \gamma_1 \log D_1 + S_1^* \quad (28)$$

Die relative Änderung der Schwarzung wird also

$$S_r = \frac{\gamma_1 \log(D_0 + \Delta D) - \gamma_0 \log D_0 + S_1^* - S_0^*}{\gamma_0 \log D_0 + S_0^*} \quad (29)$$

Die Gleichung der Aufnahme Anfertigung wird nun so erhalten dass in (29) $S_r = \Pi$ substituiert wird

$$\left[\Delta_1 \log D_0 + \Delta S^* + \gamma_1 \log (1 + D_r) = 0 \right] \quad (30)$$

oder umgeordnet und den Zusammenhang (22) substituierend, zum Schluss

$$\frac{\gamma_r}{1 + \gamma_r} \log D_0 + \frac{\Delta S^*}{\gamma_0 (1 + \gamma_r)} = - \log \frac{\eta_1 (1 + U_r) (1 + Q_r)}{\eta_0 (1 + G_{1r})} \quad (31)$$

Da in (31) sämtliche Faktoren zur Anfertigung der Aufnahme vorhanden sind können wir sie als die allgemeine Gleichung der Aufnahme Anfertigung betrachten

Zum Schluss bemerken wir dass die Struktur im Falle der Rontgendurchleuchtung sehr einfach wird da in diesem Falle, infolge der Linearität der Detektierung und der Übertragung

$$(1 + G_{1r}) = \frac{\eta_1}{\eta_0} (1 + U_r) (1 + I_r) \text{ wird}$$

ZUSAMMENFASSUNG

Das Hauptziel der Röntgentechnik ist die Informationsgewinnung. Mit Kenntnis der Aufbaukomponente des Informationsgewinnungsprozesses kann ein vereinfachtes Modell für die Röntgentechnik aufgestellt werden. Mit Hilfe dieses Modells können alle Einzelfaktoren graphisch dargestellt und mathematisch formuliert werden, mit anderen Worten die Struktur des Informationsgewinnungsprozesses erkannt und festgelegt werden.

SUMMARY

The main aim of roentgenography is to obtain information. With knowledge of the constitutional elements in the information retrieval process a simplified model for roentgen techniques may be set up. With the aid of this model the characteristic relationships may be accounted for graphically and mathematically expressed in formulas which describe the structure of the information retrieval process.

RÉSUMÉ

Le but principal de la technique radiologique est l'obtention d'information. Connaissant les composants constitués du processus d'obtention d'information on peut établir un modèle simplifié pour la technique radiologique. Grâce à ce modèle on peut déterminer les relations caractéristiques par des méthodes graphiques et exprimer leurs rapports en formules mathématiques, en d'autres termes la structure du processus d'obtention de l'information.

SCHRIFTUM

- BIERNAN A and HONDIUS BOLDINGH W The relation between tension and exposure times in radiography Acta radiol 35 (1951) 22
- CSEPINSZKY L Röntgen felvételtechnika szabályozás elmélete (In Hungarian) Elektro technika 57 (1964) 69
- FRANKE H Die Norm im Röntgenbild Fortschr Röntgenstr 14 (1931) 691
— Die historische Entwicklung der automatischen Belichtung von Röntgenaufnahmen Röntgenblätter 6 (1953), 183
- KUNTKE A H G Untersuchungen über die Änderung der Röntgenstrahlen Ausbeute an Drehanoden Röntgenrohren Fortschr Röntgenstr 87 (1957) 397
- SIIKA T Über die Standardisierung der Belichtungstechnik durch ein Punktsystem und ihre speziellen ko linearen Nomogramme Fortschr Röntgenstr 98 (1963) 216
- STIFVE I E Über die Dominante im Röntgenbild Fortschr Röntgenstr 87 (1957), 80
- WIDENMANN L, WEMBER M und SCHOTT O Untersuchungen über den Einfluss des Strahlen reliefs auf die mittlere Filmschwärzung — eine bei Belichtungsautomaten auftretende Fragestellung Röntgen Bl 15 (1962) 97

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